INVANZ®

ertapenem for injection, 1 g /vial (as ertapenem sodium)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous Intramuscular	1 g ertapenem/vial (as ertapenem sodium)	sodium bicarbonate and sodium hydroxide This is a complete listing of nonmedicinal ingredients.

INDICATIONS AND CLINICAL USE

Treatment

INVANZ® (ertapenem sodium) is indicated for the treatment of patients with the following moderate to severe infections caused by susceptible strains of the designated microorganisms (see DOSAGE AND ADMINISTRATION).

Complicated intra-abdominal infections due to *Escherichia coli*, *Clostridium clostridioforme*, *Eubacterium lentum*, *Peptostreptococcus* species, *Bacteroides fragilis, Bacteroides distasonis, Bacteroides ovatus, Bacteroides uniformis*, or *Bacteroides thetaiotaomicron*.

Complicated skin and skin-structure infections due to *Staphylococcus aureus* (methicillin- susceptible strain only), *Streptococcus pyogenes, Escherichia coli* and *Peptostreptococcus* species, as well as, diabetic foot infections due to *Staphylococcus aureus* (methicillin-susceptible strain only) and *Peptostreptococcus* species. INVANZ® has not been studied in diabetic foot infections with concomitant osteomyelitis or severe ischemia (see CLINICAL TRIALS).

Community-acquired pneumonia due to *Streptococcus pneumoniae* (penicillin-susceptible strain only), *Haemophilus influenzae* (β-lactamase negative strain only), or *Moraxella catarrhalis*.

Complicated urinary tract infections including pyelonephritis due to *Escherichia coli*, *Klebsiella pneumoniae* or *Proteus mirabilis*.

Acute pelvic infections including postpartum endomyometritis, septic abortion and post- surgical gynecologic infections due to *Streptococcus agalactiae*, *Escherichia coli*, *Peptostreptococcus* species, *Bacteroides fragilis*, *Porphyromonas asaccharolytica*, or *Prevotella* species.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of INVANZ® and other antibacterial drugs, INVANZ® should be used only to treat 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 the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to ertapenem. Initial therapy with INVANZ® may be instituted empirically for the treatment of bacterial infections, including mixed infections, while awaiting the results of these tests. Once these results become available, antimicrobial therapy should be adjusted accordingly.

Prevention

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

CONTRAINDICATIONS

INVANZ® (ertapenem sodium) 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. For a complete listing of components, see the Dosage Forms, Composition and Packaging section of the product monograph.

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 Product Monograph for lidocaine HCl).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) AND OTHER SERIOUS SKIN REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH BETA-LACTAMS, INCLUDING INVANZ® (see WARNINGS AND PRECAUTIONS, Hypersensitivity and ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Seizures and other CNS (Central Nervous System) adverse experiences have been reported during treatment with INVANZ®. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function (see WARNINGS AND PRECAUTIONS, Neurologic, Renal and ADVERSE REACTIONS).

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 serum 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. In some cases of co-administration of ertapenem with valproic acid, breakthrough seizures have occurred. 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.)

General

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.

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

Lidocaine HCl is the diluent for intramuscular administration of INVANZ®. Refer to the Product Monograph for lidocaine HCl for additional precautions.

Gastrointestinal

Clostridium difficile-associated disease

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including ertapenem. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *Clostridium difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated; as surgical intervention may be required in certain severe cases (see ADVERSE REACTIONS).

Hepatic Insufficiency

The pharmacokinetics of ertapenem in patients with hepatic insufficiency have not been established. Of the total number of patients in clinical studies, 37 patients receiving ertapenem 1 g daily and 36 patients receiving comparator drugs were considered to have Child-Pugh Class A, B or C liver impairment. The incidence of adverse experiences in patients with hepatic impairment was similar between the ertapenem group and the comparator groups.

Hypersensitivity

SERIOUS AND OCCASIONALLY FATAL HYPESENSITIVITY (ANAPHYLACTIC) AND OTHER SERIOUS SKIN REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING BETA-LACTAM ANTIBIOTICS, INCLUDING INVANZ®. HYPERSENSITIVITY (ANAPHYLACTIC) 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. CROSS-REACTIVITIES BETWEEN BETA-LACTAM ANTIBIOTICS HAVE BEEN CLEARLY DOCUMENTED. BEFORE INITIATING THERAPY WITH INVANZ® (ERTAPENEM SODIUM), 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 WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION. OTHER THERAPY MAY ALSO BE ADMINISTERED AS INDICATED** (see CONTRAINDICATIONS and ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Neurologic

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 (see ADVERSE REACTIONS). 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, placed on anticonvulsant therapy if not already instituted, and the dosage of INVANZ® re-examined to determine whether it should be decreased or the antibiotic discontinued (see ADVERSE REACTIONS).

Renal

Dosage adjustment of INVANZ® is recommended in patients with reduced renal function (see DOSAGE AND ADMINISTRATION). A supplementary dose may be recommended in patients following hemodialysis (see DOSAGE AND ADMINISTRATION, Patients on Hemodialysis).

Susceptibility/Resistance

Development of Drug Resistant Bacteria

Prescribing INVANZ® in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Special Populations

Pregnant Women: 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.

Nursing Women: Ertapenem is excreted in human milk. INVANZ® should be administered to nursing mothers only when the potential benefit outweighs the potential risk (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Pediatrics (< 18 years of age): 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 USE and CLINICAL TRIALS, Pediatric Patients).

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

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.

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

This drug 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 (see DOSAGE AND ADMINISTRATION).

Monitoring and Laboratory Tests

While INVANZ® possesses toxicity similar to the beta-lactam group of antibiotics, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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® (ertapenem sodium). 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.

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%).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adult Patients

Table 1 shows the incidence of drug-related adverse experiences reported during parenteral therapy.

Table 1: Incidence (%) of Drug-Related Adverse Experiences* Reported During Parenteral Therapy in ≥ 1.0% of Adult Patients Treated with INVANZ® in Clinical Studies

Adverse Events	INVANZ® 1 g daily (N=1866)	Piperacillin/ Tazobactam 3.375 g q6h (N=775)	Ceftriaxone 1 or 2 g daily (N=912)
Gastrointestinal disorders:			
Diarrhea	4.3	6.6	3.7
Nausea	2.9	3.2	2.6
Vomiting	1.0	1.5	0.9
General disorders and administration site conditions:			
Infused vein complication	3.9	5.5	4.3
Nervous system disorders:			
Headache	2.1	1.0	2.2
Vascular disorders:			
Phlebitis/thrombophlebitis	1.3	1.3	1.4

* Determined by the investigator to be possibly, probably, or definitely drug-related.

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.

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

Table 2 lists the less common drug-related adverse experiences that were reported during parenteral therapy with INVANZ® within each body system.

Table 2: Less Common Clinical Trial Adverse Drug Reactions (< 1%) in Adult Patients

System Organ Class	Uncommon Clinical Trial Adverse Drug Reactions (≥ 0.1% but < 1.0%) Ertapenem (N=1866)	Rare Clinical Trial Adverse Drug Reactions (< 0.1%) Ertapenem (N=1866)
Blood and lymphatic system disorders		eosinophilia, neutropenia, thrombocytopenia
Cardiac disorders		arrhythmia, tachycardia
Gastrointestinal disorders	Acid regurgitation, constipation, *C. difficile*-associated diarrhea, dry mouth, dyspepsia	colitis, dysphagia, tongue edema, flatulence, gastritis, gastric ulcer, fecal incontinence, mouth ulcer, pelvic peritonitis
General disorders and administration site conditions	Asthenia/fatigue, edema/swelling, fever, pain, abdominal pain, chest pain, extravasation, candidiasis, taste perversion.	chills, cold extremities, facial edema, injection site induration, injection site stinging, malaise, thirst, warm sensation
Hepatobiliary disorders		cholecystitis, jaundice, liver disorder
Immune system disorders		Allergy
Infections and infestations	Oral candidiasis	cellulitis, dermatomycosis, fungal infection, herpes simplex, postoperative wound infection, urinary tract infection
Injury, poisoning and procedural complications		drug overdose
Investigations		increased blood pressure
Metabolism and nutrition disorders	Anorexia	hypoglycemia
Musculoskeletal and connective tissue disorders		muscle cramps, elbow pain, shoulder pain
Nervous system disorders	Confusion, dizziness, insomnia, somnolence, seizures	restless leg syndrome, grand mal seizure, parasthesia, tremor
Pregnancy, puerperium and perinatal conditions		abortion
Psychiatric disorders		agitation, anxiety, depression, hallucinations, syncope
Renal and urinary disorders		acute renal insufficiency, renal insufficiency
Reproductive system and breast disorders	Vaginal pruritus	genital bleeding, vaginal dryness
Respiratory, thoracic and mediastinal disorders	Dyspnea	nasal congestion, cough, epistaxis, pharyngeal discomfort, pneumonia, rales/rhonchi, wheezing
Skin and subcutaneous tissue disorders	Erythema, pruritus	dermatitis, desquamation
Vascular disorders	Hypotension	flushing, hot flashes, vasculitis

Pediatric Patients

Table 3 shows the incidence of drug-related adverse experiences reported during parenteral therapy.

Table 3: Incidence (%) of Drug-Related Adverse Experiences* Reported During Parenteral Therapy in ≥ 1.0% of Pediatric Patients Treated with INVANZ® in Clinical Studies

Adverse Events	INVANZ® (N=384)	Ceftriaxone (N=100)	Ticarcillin/clavulanate (N=24)
Gastrointestinal disorders:			
Diarrhea	5.5	10.0	4.2
Vomiting	1.6	2.0	0.0
General disorders and administration site conditions:			
Infusion site erythema	2.6	2.0	0.0
Infusion site pain	5.5	1.0	12.5
Infusion site phlebitis	1.8	3.0	0.0
Infusion site swelling	1.0	0.0	0.0
Skin and subcutaneous tissue disorders:			
Rash	1.3	1.0	4.2

* Determined by the investigator to be possibly, probably or definitely drug-related.

In the pediatric clinical studies, the majority of the patients had parenteral therapy followed by a switch to an appropriate oral antimicrobial (see CLINICAL TRIALS). During the entire treatment period and a 14 day post-treatment follow-up period, drug-related adverse experiences reported with an incidence of ≥ 1.0% in patients treated with INVANZ® were no different than those listed in Table 3.

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

Additional drug-related adverse experiences that were reported during parenteral therapy with INVANZ® with an incidence of > 0.2% but < 1% in pediatric studies within each body system are listed below in Table 4:

Table 4: Less Common Clinical Trial Adverse Drug Reactions (> 0.2% but < 1%) in Pediatric Patients

System Organ Class	Ertapenem (N=384)
Gastrointestinal	abdominal pain, enteritis, flatulence, loose stools, nausea, toothache
General disorders and administration site conditions	chest pain, hypothermia, infusion site burning, infusion site induration, infusion site oedema, infusion site pruritus, infusion site reaction, infusion site warmth, injection site bruising, injection site erythema
Infections and infestations	oral candidiasis
Metabolism and nutritional	decreased appetite
Nervous system	headache
Reproductive system and breast disorders	genital rash
Respiratory, thoracic and mediastinal disorders	wheezing
Skin and subcutaneous tissue disorders	dermatitis diaper, erythema, petechiae, pruritus, rash erythematous, rash macular
Vascular disorders	hot flash, hypertension, phlebitis

Laboratory Test Findings

Adult Patients

Table 5 shows the most frequently observed drug-related laboratory abnormalities during parenteral therapy in patients receiving INVANZ®.

Table 5: Incidence* (%) of Specific Drug-Related Laboratory Adverse Experiences Reported During Parenteral Therapy in ≥ 1.0% of Adult Patients Treated With INVANZ® in Clinical Studies

Laboratory adverse experiences	INVANZ® 1 g daily n†=1766	Piperacillin/Tazobactam 3.375 g q6h n†=750	Ceftriaxone 1 or 2 g daily n†=870
Chemistry:			
ALT ↑	5.5	4.4	4.9
AST ↑	4.8	4.5	4.2
Alkaline phosphatase ↑	2.9	3.9	1.4
Hematology:			
Platelet count ↑	2.0	3.9	0.4

* Number of patients with laboratory adverse experiences/Number of patients with the laboratory test; where at least 1516 patients had the test.
† Number of patients with one or more laboratory tests.

Other drug-related laboratory abnormalities that were reported during parenteral therapy in > 0.1% but < 1.0% of patients treated with INVANZ® in clinical studies included the following:

Chemistry: increases in direct serum bilirubin, total serum bilirubin, indirect serum bilirubin, BUN, serum creatinine, serum glucose

Hematology: increases in eosinophils, PTT, monocytes; decreases in segmented neutrophils, white blood cells, hematocrit, hemoglobin and platelet count

Urinalysis: increases in urine bacteria, urine epithelial cells, urine red blood cells.

In the majority of clinical studies, parenteral therapy was followed by a switch to an appropriate oral antimicrobial (see CLINICAL TRIALS). During the entire treatment period and a 14-day post- treatment follow-up period, drug-related laboratory abnormalities in patients treated with INVANZ® were no different than those listed in Table 5.

Pediatric Patients

Table 6 shows the most frequently observed drug-related laboratory abnormality during parenteral therapy in patients receiving INVANZ®.

Table 6: Incidence* (%) of Specific Drug-Related Laboratory Adverse Experiences Reported During Parenteral Therapy in ≥ 1.0% of Pediatric Patients Treated With INVANZ® in Clinical Studies

Laboratory adverse experiences	INVANZ® (N†=384)	Ceftriaxone (N†=100)	Ticarcillin/clavulanate (N†=24)
Chemistry:			
ALT ↑	1.9	0.0	4.3
AST ↑	1.9	0.0	4.3
Hematology:			
Neutrophil count ↓	2.5	1.1	0.0

* Number of patients with laboratory adverse experiences/Number of patients with the laboratory test; where at least 300 patients had the test.
† Number of patients with one or more laboratory tests.

Additional drug-related laboratory adverse experiences that were reported during parenteral therapy in > 0.5% but < 1.0% of pediatric patients treated with INVANZ® in clinical studies include: increase in eosinophils.

Prevention

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 and 476 adult patients received a 2 g dose of cefotetan prior to surgery, the following additional (i.e., in addition to Adverse Experiences listed in Table 1) drug-related adverse experience was reported with an incidence of ≥ 1.0% (common): wound infection (1.7% for patients treated with ertapenem and 2.1% for patients treated with cefotetan).

The following additional (i.e., in addition to Adverse Experiences listed in Table 2) drug-related adverse experiences were reported with an incidence of < 1.0% (uncommon) as listed below:

Cardiac disorders: Sinus bradycardia

Infections and infestations: Cellulitis, clostridial infection, *Clostridium* colitis, postoperative infection

Injury and poisoning: Wound complication

Skin and subcutaneous tissue disorders: Erythematous rash, urticaria.

The following additional (i.e., in addition to adverse experiences listed in the Laboratory Test Findings Section) drug related laboratory adverse experiences were reported with an incidence of < 1.0% (uncommon): increases in white blood cells and prothrombin time (PT).

Patients with Renal Insufficiency

There are limited data in adults patients with renal insufficiency from the study of prophylaxis of surgical site infection following elective colorectal surgery. In a clinical study in which 476 treated patients received a 1 g dose of ertapenem 1 hour prior to surgery, the AE profile observed in five patients with creatinine clearance ≤ 30 mL/min./1.73 m^2 is consistent with their underlying renal condition and/or having just undergone major elective colorectal surgery.

Post-Market Adverse Drug Reactions

The following additional post-marketing adverse experiences have been reported:

Gastrointestinal Disorders: teeth staining

Immune System: anaphylaxis including anaphylactoid reactions.

Musculoskeletal and Connective Tissue Disorders: muscular weakness.

Nervous System Disorders: depressed level of consciousness, dyskinesia, gait disturbance, myoclonus, tremor.

Psychiatric Disorders: altered mental status (e.g., aggression, agitation, confusion/confusional state, delirium, disorientation, mental status changes), hallucinations.

Skin and Subcutaneous Tissue Disorders: Acute Generalized Exanthematous Pustulosis (AGEP), Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome),.

DRUG INTERACTIONS

Overview

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 that ertapenem does not inhibit metabolism mediated by any of the following six 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 with the listed isoforms are unlikely (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics). *In vitro* studies indicate that ertapenem, over its therapeutic concentration range, has little effect on the unbound fraction of warfarin in human plasma.

Drug-Drug Interactions

Probenecid

When ertapenem is administered with probenecid (500 mg of probenecid every 6 hours), probenecid competes for active tubular secretion and reduces the renal excretion of ertapenem. This leads to small but statistically significant increases in the elimination half-life (19%, mean half-life with probenecid is 4.8 hours and mean half-life without probenecid is 4.0 hours) and in the extent of systemic exposure (25%, mean $AUC_{0-\infty}$ of total ertapenem with probenecid is 767.6 µg•hr/mL and mean $AUC_{0-\infty}$ of total ertapenem without probenecid is 616.2 µg•hr/mL). The coadministration of ertapenem with probenecid is not recommended, unless clinically necessary, due to the small effect on half-life. No dosage adjustment is recommended when patients receive probenecid concomitantly with ertapenem.

Valproic Acid

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 serum 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. In some cases of co-administration of ertapenem with valproic acid, breakthrough seizures have occurred. The mechanism of this interaction is unknown (see WARNINGS AND PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Treatment

Recommended Dose and Dosage Adjustment

The recommended dose of INVANZ® (ertapenem sodium) in patients 13 years of age and older is 1 gram (g) given once a day. The recommended dose of INVANZ® in patients 3 months to 12 years of age is 15 mg/kg twice daily (not to exceed 1 g/day).

Table 7 presents treatment guidelines for INVANZ®.

Table 7: Daily Treatment Guidelines for Adult and Pediatric Patients with Normal Renal Function*

Infection†	Patients 13 years of age and older	Patients 3 months to 12 years of age	Recommended Duration of Total Antimicrobial Treatment
Complicated Intra-abdominal Infections	1 g daily	15 mg/kg/dose to a maximum of 500 mg twice daily§	5 to 14 days
Complicated Skin and Skin-Structure Infections	1 g daily	15 mg/kg/dose to a maximum of 500 mg twice daily§	7 to 14 days
Diabetic foot infections	1 g daily (patients ≥ 18 years old only)	not applicable	5 to 28 days‡
Community-Acquired Pneumonia	1 g daily	15 mg/kg/dose to a maximum of 500 mg twice daily§	10 to 14 days‡
Complicated Urinary Tract Infections including pyelonephritis	1 g daily	15 mg/kg/dose to a maximum of 500 mg twice daily§	10 to 14 days‡
Acute Pelvic Infections including postpartum endomyometritis, septic abortion and post- surgical gynecologic infections	1 g daily	15 mg/kg/dose to a maximum of 500 mg twice daily§	3 to 10 days

* Defined as creatinine clearance > 90 mL/min/1.73 m^2.
† Due to the designated pathogens (see INDICATIONS AND CLINICAL USE).
‡ Duration includes a possible switch to an appropriate oral therapy once clinical improvement has been demonstrated.
§ Not to exceed 1 g/day.

Special Populations

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 (SI = > 0.5 mL/s/1.73 m^2), no dosage adjustment is necessary. Adult patients with advanced renal insufficiency (creatinine clearance ≤ 30 mL/min/1.73 m^2 (SI = ≤ 0.5 mL/s/1.73 m^2)), and end-stage renal insufficiency on hemodialysis (creatinine clearance ≤ 10 mL/min/1.73 m^2 (SI = ≤ 0.17 mL/s/1.73 m^2)) **should receive 500 mg daily**. There are no data in pediatric patients with renal insufficiency. This recommended dosage reduction is based on pharmacokinetic modeling of data collected from a clinical safety and pharmacokinetic study in adult patients with varying degrees of renal insufficiency (including those with creatinine clearance < 30 mL/min/1.73 m^2 (SI = < 0.5 mL/s/1.73 m^2)) receiving a single 1 g IV dose of ertapenem (see ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency). The efficacy of the recommended adjusted dose (500 mg) for adult patients with advanced or end- stage renal insufficiency has not been established.

Patients on Hemodialysis

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 recommended. 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 (mL/min). 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)

When using the International System of units (SI), the estimated creatinine clearance (mL/s) can be calculated as follows:

Males: $\frac{\text{(weight in kg) x (140-age in years) x 1.4736}}{\text{(72) x serum creatinine (µmol/L)}}$

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

Patients with Hepatic Impairment
No dosage adjustment recommendation can be made in patients with impaired hepatic function (see ACTION AND CLINICAL PHARMACOLOGY, Special Population and WARNINGS AND PRECAUTIONS, Hepatic Insufficiency).

Age/Gender
No dosage adjustment is recommended based on age (**13 years of age and older**) or gender. Dosing adjustment is needed based on age 3 months to 12 years of age (see ACTION AND CLINICAL PHARMACOLOGY, Special Population and WARNINGS AND PRECAUTIONS, Pediatrics).

Prevention
Table 8 presents prophylaxis guidelines for INVANZ®.

Table 8: Prophylaxis Guidelines for Adults

Indication	Daily Dose (IV) Adults	Recommended Duration of Total Antimicrobial Treatment
Prophylaxis of surgical site infection following elective colorectal surgery*	1 g	Single intravenous dose given 1 hour prior to the surgical incision

* Limited data are available in patients with advanced renal insufficiency (creatinine clearance ≤ 30 mL/min/1.73 m² [SI = ≤ 0.5 mL/s/1.73 m²]) (see ADVERSE REACTIONS, Prevention, Patients with Renal Insufficiency).

Missed Dose
The injection schedule will be set by the physician, who will monitor the response and condition to determine what treatment is needed.

Administration
INVANZ® may be administered by intravenous infusion or intramuscular 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.

Reconstitution

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).

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

INVANZ® MUST BE RECONSTITUTED AND THEN DILUTED PRIOR TO ADMINISTRATION.

I. Reconstitute the contents of a 1 g vial of INVANZ® with 10 mL Water for Injection, 0.9% Sodium Chloride Injection or Bacteriostatic Water for Injection to yield a reconstituted solution of approximately 100 mg/mL. Shake well to dissolve.
II. To withdraw a 1 gram dose, immediately withdraw 9.8 mL of the reconstituted vial and transfer to 50 mL of 0.9% Sodium Chloride Injection.
III. The reconstituted IV solution should be used within 6 hours after preparation.

Preparation for Intramuscular Administration:
INVANZ® MUST BE RECONSTITUTED PRIOR TO ADMINISTRATION.

I. Reconstitute the contents of a 1 g vial of INVANZ® with 3.2 mL of 1.0% lidocaine HCl injection*** (**without epinephrine**) to yield a reconstituted solution of approximately 280 mg/mL. Shake vial thoroughly to form solution. To withdraw a 1 gram dose, the contents of the reconstituted vial should be withdrawn as completely as possible.
II. 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).
III. The reconstituted IM solution should be used within 1 hour after preparation.
Note: The reconstituted solution should not be administered intravenously.

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.

I. Reconstitute the contents of a 1 g vial of INVANZ® with 10 mL Water for Injection, 0.9% Sodium Chloride Injection or Bacteriostatic Water for Injection to yield a reconstituted solution of approximately 100 mg/mL. Shake well to dissolve.
II. Immediately withdraw a volume equal to 15 mg/kg of body weight (not to exceed 500 mg per dose) and dilute in 0.9% Sodium Chloride Injection to a final concentration of 20 mg/mL or less (not to exceed 1g/day).
III. The reconstituted IV solution should be used within 6 hours after preparation. Discard unused portion of the vial.

Preparation for Intramuscular Administration:
INVANZ® MUST BE RECONSTITUTED PRIOR TO ADMINISTRATION.

I. Reconstitute the contents of a 1 g vial of INVANZ® with 3.2 mL of 1.0% lidocaine HCl injection*** (**without epinephrine**) to yield a reconstituted solution of approximately 280 mg/mL. Shake vial thoroughly to form solution.
II. Immediately withdraw a volume equal to 15 mg/kg of body weight (not to exceed 500 mg per dose and 1g/day) and administer by deep intramuscular injection into a large muscle mass (such as the gluteal muscles or lateral part of the thigh).
III. The reconstituted IM solution should be used within 1 hour after preparation.
Note: The reconstituted solution should not be administered intravenously. Discard unused portion of the vial.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use, whenever solution and container permit. As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used. Discard unused portion. Solutions of INVANZ® range from colorless to pale yellow. Variations of color within this range do not affect the potency of the product.

The vials are for single use only. Unused portions should be discarded.

OVERDOSAGE

For management of suspected drug overdose, consult your regional Poison Control Centre.

No specific information is available on the treatment of overdosage with INVANZ® (ertapenem sodium). 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
INVANZ® (ertapenem sodium) is a sterile, synthetic, parenteral, 1-ß methyl-carbapenem that is structurally related to beta-lactam antibiotics, such as penicillins and cephalosporins, with *in vitro* activity against a range of gram-positive and gram-negative aerobic and anaerobic bacteria.

*** Refer to the prescribing information for lidocaine HCl

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

Pharmacokinetics
Overall, ertapenem pharmacokinetics were approximately linear. The plasma concentration of total ertapenem declines in a poly-exponential fashion following single 30-minute intravenous infusion. Area under the plasma concentration curve (AUC) of ertapenem increased slightly less than dose- proportionally based on total ertapenem concentrations over the 0.5 to 2 g dose range and that the AUC increased slightly greater than dose proportionally based on unbound ertapenem concentrations over the 0.5 to 2 g dose range. The slight deviations from strict dose proportionality are thought to be due to concentration-dependent plasma protein binding at the proposed therapeutic dose. The departure from dose-proportionality is very slight and, given the apparent wide therapeutic index of ertapenem, is not considered clinically relevant. The apparent volume of distribution of ertapenem at steady state is approximately 8.2 liters. The major metabolite of ertapenem is the bacteriologically inactive ring-opened derivative formed predominantly by the kidney by hydrolysis of the beta-lactam ring. Ertapenem is eliminated primarily by the kidneys. Plasma radioactivity consists predominantly (94%) of ertapenem. The mean plasma half-life of ertapenem 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. The mean bioavailability of 1 g IM dose is approximately 92%. There is no accumulation of ertapenem following multiple IV doses ranging from 0.5 to 2 g daily or IM doses of 1 g daily.

Average plasma concentrations (µg/mL) and mean $AUC_{0-\infty}$ of total 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 9.

Table 9: Plasma Concentrations and Mean $AUC_{0-\infty}$ of Total Ertapenem After Single Dose Administration in Healthy Young Adults

Route/Dose	Average Plasma Concentrations (µg/mL)									$AUC_{0-\infty}$ (µg•hr/mL)
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	18 hr	24 hr	
IV 1 g*	155	115	83	48	31	20	9	3	1	572
IV 2 g*	283	202	145	86	58	36	16	5	2	1011
IM 1 g	33	53	67	57	40	27	13	4	2	555

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

Mean $AUC_{0-\infty}$ values (µg•hr/mL) of unbound ertapenem for intravenous doses of 1 g and 2 g are 33.2 and 76.6, respectively.

Average plasma concentrations (µg/mL) of ertapenem in pediatric patients are presented in Table 10.

Table 10: Plasma Concentrations of Ertapenem in Pediatric Patients After Single IV* Dose Administration

Age Group (Dose)	Average Plasma Concentrations (µg/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 1g/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

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 (mean Cmax = 70.6 µg/mL) are reached in approximately 2 hours (mean Tmax = 2.2 hours) [see Table 9].

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

The apparent volume of distribution (V_{ss}) of ertapenem in adults at steady state is approximately 8.2 liters (0.12 liter/kg), approximately 0.2 liter/kg in pediatric patients 3 months to 12 years of age and approximately 0.16 liter/kg in pediatric patients 13 to 17 years of age.

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 11. The ratio of $AUC_{0\text{-}24hr}$ of total ertapenem in skin blister fluid to $AUC_{0\text{-}24hr}$ of total ertapenem in plasma is 0.61.

Table 11: Concentrations (µg/mL) of Total 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 concentration 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 a 3- to 6-day, once daily 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 µg/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 µg/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).

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 bacteriologically inactive ring-opened derivative formed predominantly by the kidney by hydrolysis of the beta-lactam ring. This metabolite is found in urine (approximately 37% of the administered dose).

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). *In vitro* studies in human liver microsomes indicate that ertapenem is a poor substrate of cytochrome P450 (CYP) isoforms.

Coadministration of cilastatin (renal dehydropeptidase-1 inhibitor) significantly reduced the plasma clearance of ertapenem and increased the urinary excretion of ertapenem in rats and mice consistent with the view that dehydropeptidase-1 catalyzed the metabolism of ertapenem.

Excretion: 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 bacteriologically inactive ring-opened metabolite.

In healthy young adults given a 1 g IV dose, average concentrations of ertapenem in urine exceed 984 µg/mL during the period 0 to 2 hours postdose and exceed 52 µg/mL during the period 12 to 24 hours postdose.

Special Populations and Conditions

Pediatrics: 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 shows 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 ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics 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 1g IV dose of ertapenem.

Geriatrics: Plasma concentrations (AUC) following a 1 g and 2 g IV dose of ertapenem are slightly higher (approximately 39% and 22% for total ertapenem, respectively, and approximately 71% and 65% for unbound ertapenem, respectively) in elderly adults (≥ 65 years) relative to young adults (< 65 years). These differences could be attributed partly to age-related changes in renal function. No dosage adjustment is necessary for elderly patients with normal (for their age) renal function.

Gender: The plasma concentration profiles of ertapenem are comparable in healthy men and women when body weight differences are taken into consideration. No dosage adjustment is recommended based on gender.

Hepatic Insufficiency: The pharmacokinetics of ertapenem in patients with hepatic insufficiency have not been established. In vitro studies indicate that ertapenem is metabolically stable in human liver microsomes. Following administration of a 1 g radiolabeled IV dose of ertapenem to healthy young adults, only 10% of ^{14}C-ertapenem was recovered in feces (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Metabolism and Excretion). Due to the limited extent of hepatic metabolism of ertapenem, its pharmacokinetics are not expected to be affected by hepatic impairment. No dosage adjustment recommendations can be made in patients with hepatic impairment.

Renal Insufficiency: Single 1 g IV doses of ertapenem were administered to 26 adult subjects with varying degrees of renal impairment, AUC was similar in patients with mild renal insufficiency (Cl_{cr} 60–90 mL/min/1.73 m² (when using International System of Units (SI), SI = 1.0–1.5 mL/s/1.73 m²)) compared with healthy subjects (ages 25 to 82 years). AUC was increased in patients with moderate renal insufficiency (Cl_{cr} 31–59 mL/min/1.73 m² (SI = 0.52–0.98 mL/s/1.73 m²)) approximately 1.5-fold compared with healthy subjects. AUC was increased in patients with advanced renal insufficiency (Cl_{cr} 5–30 mL/min/1.73 m² (SI = 0.08–0.50 mL/s/1.73 m²)) approximately 2.6-fold compared with healthy subjects. AUC was increased in patients with end-stage renal insufficiency (Cl_{cr} < 10 mL/min/1.73 m² (SI = < 0.17 mL/s/1.73 m²)) approximately 2.9-fold compared with healthy subjects. There are no data in pediatric patients with renal insufficiency.

A dosage adjustment (500 mg once daily) is recommended for adult patients with advanced or end- stage renal insufficiency (see DOSAGE AND ADMINISTRATION). The recommended dosage reduction is based on pharmacokinetic modeling of data collected from the clinical safety and pharmacokinetic study in patients with varying degrees of renal insufficiency (including those with creatinine clearance < 30 mL/min/1.73 m² (SI = < 0.5 mL/s/1.73 m²)) receiving a single 1 g IV dose of ertapenem. Pharmacokinetic modeling was used to determine a dosing regimen, which would provide equivalent drug exposure for which clinical efficacy has been demonstrated.

Following a single 1 g IV dose in 5 patients with end-stage renal insufficiency given immediately prior to a 4-hour hemodialysis session, approximately 30% of the dose was recovered in the dialysate. When patients on hemodialysis are given the recommended daily dose of 500 mg of INVANZ® (ertapenem sodium) within 6 hours prior to hemodialysis, a supplementary dose of 150 mg is recommended following the hemodialysis session (see DOSAGE AND ADMINISTRATION).

Table 12 displays the mean plasma AUCs and the geometric mean AUC ratios (RI/Pooled Control) for total and unbound ertapenem in adult patients with varying degrees of renal insufficiency (RI).

Table 12: Mean Plasma AUCs and Geometric Mean Ratios (GMR) for Total and Unbound Ertapenem Following a 1 g Intravenous Dose of Ertapenem in Adult Patients with Varying Degrees of Renal Insufficiency (RI) Versus the Pooled Control Group

Pharmacokinetic Parameter	Pooled Control*	Mild RI†	Moderate RI†	Advanced RI†	End-Stage RI†
Total drug					
$AUC_{0-\infty}$ (µg•hr/mL)	665.9	712.2	1016.5	1719.9	1941.5
GMR‡	--	1.1	1.5	2.6	2.9
Unbound drug					
$AUC_{0-\infty}$ (µg•hr/mL)	42.5	44.2	76.1	144.6	252.7
GMR	--	1.0	1.8	3.4	6.0

* Pooled Control: Healthy young adult and healthy elderly subjects.
† Mild RI = Cl_{cr} 60–90 mL/min/1.73 m²; Moderate RI = Cl_{cr} 31–59 mL/min/1.73 m²; Advanced RI= Cl_{cr} 5–30 mL/min/1.73 m²; End-Stage RI = Cl_{cr} < 10 mL/min/1.73 m².
‡ GMR = Geometric Mean Ratio of RI/Pooled Control.

STORAGE AND STABILITY

Before Reconstitution
Do not store above 25°C..

Reconstituted and Infusion Solutions
The reconstituted solution, immediately diluted in 0.9% Sodium Chloride Injection (see DOSAGE AND ADMINISTRATION, Administration), 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® (ertapenem sodium) should not be frozen (see DOSAGE AND ADMINISTRATION, Reconstitution).

DOSAGE FORMS, COMPOSITION AND PACKAGING

INVANZ® (ertapenem sodium) is supplied as a sterile lyophilized powder in single dose glass vials containing 1 g of ertapenem as free acid for intravenous infusion or for intramuscular injection.

Each vial of INVANZ® contains the following inactive ingredients: sodium bicarbonate and sodium hydroxide to adjust pH to 7.5. The sodium content is approximately 137 mg (approximately 6.0 mEq).

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(THIS IS A MEDICAMENT)
- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor. Keep medicament out of reach of children
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