

Name of Medicine

INVANZ[®]

ertapenem sodium

1 gram injection

Presentation

INVANZ is supplied as a sterile white to off-white lyophilised powder for intravenous infusion or intramuscular injection.

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.

Indications

Treatment

INVANZ is indicated for the treatment of patients with moderate to severe infections caused by susceptible strains of micro-organisms, 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 gynaecologic infections
- Bacterial Septicaemia

Prevention

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

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 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 m², no dosage adjustment is necessary. Adult patients with advanced renal insufficiency (creatinine clearance ≤ 30 mL/min/1.73 m²), including those on haemodialysis, should receive 500 mg daily.

There are no data in paediatric patients with renal insufficiency.

Patients on Haemodialysis

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

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

Females: $(0.85) \times (\text{value calculated for males})$

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

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

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

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% 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.

Paediatric 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 the 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.

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

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

Contraindications

INVANZ is contraindicated in patients with known hypersensitivity to any component of this product or to other medicines 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 anaesthetics of the amide type and in patients with severe shock or heart block. (Refer to the prescribing information for lidocaine HCl.)

Warnings and 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 medicine immediately. Serious anaphylactic reactions require immediate emergency treatment.

The concomitant use of INVANZ and sodium valproate is not recommended (see Interactions).

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 diarrhoea 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.

Laboratory Tests

While INVANZ possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system function, including renal, hepatic, and haematopoietic, is advisable during prolonged therapy.

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 foetus.

Nursing Mothers

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

Paediatric Use

Safety and effectiveness of INVANZ in paediatric patients 3 months to 17 years of age are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in paediatric patients, and additional data from comparator-controlled studies in paediatric patients 3 months to 17 years of age with the following infections (see Indications).

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

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

Clinical studies that were conducted excluded infants under 3 months of age due to their propensity to localise infection poorly and therefore to be at increased risk of meningitis associated with septicaemia.

Efficacy of ertapenem in patients with meningitis has not been studied. In a pharmacokinetic, cerebrospinal fluid (CSF) penetration study in paediatric patients with meningitis, ertapenem demonstrated a geometric mean CSF/plasma ratio of approximately 4% but exhibited wide variability precluding its use in CSF infections. Ertapenem concentrations in CSF were not sufficient to cover all likely pathogens suggesting the potential for impaired efficacy in patients developing septicaemia with CSF infection.

Use in the Elderly

Of the total number of patients in clinical studies treated with INVANZ, approximately 25 percent were 65 and over, while approximately 12 percent were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This medicine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this medicine 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.)

Animal Toxicology

Acute Toxicology

The approximate LD₅₀ of ertapenem after a single IV dose in mice and rats was greater than the highest doses studied (700 mg/kg in rats and 2000 mg/kg in mice). There were

no deaths in either species; transient decreased activity was observed in mice given 2000 mg/kg.

Chronic Toxicology

The toxic potential of ertapenem was evaluated in a series of repeated daily IV toxicity studies of up to 6 months in monkeys and rats. There were no findings that would preclude administration at the therapeutic dosage level.

Carcinogenesis

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

Mutagenesis

Ertapenem was neither mutagenic nor genotoxic in the following *in vitro* assays: alkaline elution/rat hepatocyte assay, chromosomal aberration assay in Chinese hamster ovary cells, and TK6 human lymphoblastoid cell mutagenesis assay; and in the *in vivo* mouse micronucleus assay.

Reproduction

In mice and rats, IV doses of up to 700 mg/kg/day (for mice, approximately 3 times the recommended human dose of 1 g based on body surface area and for rats, approximately 1.2 times the human exposure at the recommended dose of 1 g based on plasma AUCs) resulted in no effects on mating performance, fecundity, fertility, or embryonic survival.

Development

In mice and rats given IV doses of up to 700 mg/kg/day (for mice, approximately 3 times the recommended human dose of 1 g based on body surface area and for rats, approximately 1.2 times the human exposure at the recommended dose of 1 g based on plasma AUCs), there was no evidence of developmental toxicity as assessed by external, visceral, and skeletal examination of the foetuses. However, in mice given 700 mg/kg/day, slight decreases in average foetal weights and an associated decrease in the average number of ossified sacrocaudal vertebrae were observed.

Ertapenem crosses the placental barrier in rats.

Ability to Drive and Use Machinery

There are no data to suggest that INVANZ affects the ability to drive and operate machinery.

Adverse 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. Medicine-related adverse experiences were reported in approximately 20% of patients treated with ertapenem. Ertapenem was discontinued due to adverse experiences thought to be medicine-related in 1.3% of patients.

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

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

Common ($\geq 1/100$, $< 1/10$)

Nervous system disorders: Headache

Vascular disorders: Infused vein complication, phlebitis/thrombophlebitis

Gastrointestinal disorders: Diarrhoea, 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: Dyspnoea

Gastrointestinal disorders: Oral candidiasis, constipation, acid regurgitation, *C. difficile*-associated diarrhoea, dry mouth, dyspepsia, anorexia

Skin and subcutaneous tissue disorders: Erythema, pruritus

General disorders and administration site conditions: Abdominal pain, taste perversion, asthenia/fatigue, candidiasis, oedema/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, medicine-related adverse experiences in patients treated with INVANZ included those listed above as well as rash and vaginitis at an incidence of $\geq 1.0\%$ (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 medicine-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 medicine-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).

Paediatric Patients

The total number of paediatric 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 medicine-related clinical adverse experiences reported during parenteral therapy were diarrhoea (5.5%), infusion site pain (5.5%) and infusion site erythema (2.6%).

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

Common ($\geq 1/100$, $< 1/10$)

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 medicine-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 paediatric 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 post treatment follow-up period, medicine-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: Dyskinesia, hallucinations, myoclonus, tremor

Skin and subcutaneous tissue disorders: Urticaria, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome)

Laboratory Test Findings

Adult Patients

The most frequently observed medicine-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, medicine-related laboratory abnormalities in patients treated with INVANZ were no different than those listed above.

Other medicine-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, haematocrit, haemoglobin 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 medicine-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 medicine-related laboratory adverse experiences reported during parenteral therapy.

Paediatric Patients

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

Other medicine-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.

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. Medicine interactions caused by inhibition of P-glycoprotein-mediated medicine clearance or CYP-mediated medicine clearance are unlikely. (See Pharmacokinetics, *Distribution* and *Metabolism*.)

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

Decreases in serum valproic acid levels that may fall below the therapeutic range, have been reported in patients co-administered sodium valproate with carbapenem agents, including ertapenem. The significant reductions in serum valproic acid levels (60% - 100%) have been reported within two days of other carbapenem administration and may lead to inadequate seizure control. Due to the rapid onset and the extent of the decrease in serum levels, co-administration of carbapenem agents in patients stabilised on sodium valproate is not considered to be manageable and should therefore be avoided.

If administration of INVANZ is necessary, alternative or supplemental anti-convulsant therapy should be considered.

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 paediatric 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 haemodialysis; however, no information is available on the

use of haemodialysis to treat overdose.

Actions

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 micro-organisms *in vitro* and in clinical infections (see Indications):

Aerobic and Facultative Anaerobic Gram-Positive Micro-organisms

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 Micro-organisms

Escherichia coli

Haemophilus influenzae (including beta-lactamase producing strains)

Klebsiella pneumoniae

Moraxella catarrhalis

Proteus mirabilis

Anaerobic Micro-organisms

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 ($\geq 90\%$) strains of *Streptococcus* species including *Streptococcus pneumoniae*, ≤ 0.5 mcg/mL against most ($\geq 90\%$) strains of *Haemophilus* species and ≤ 2 mcg/mL against most ($\geq 90\%$) strains of the other aerobic and facultative anaerobic micro-organisms and ≤ 4 mcg/mL against most ($\geq 90\%$) strains of the strict anaerobic micro-organisms in the following list; however, the safety and effectiveness of INVANZ in treating clinical infections due to these micro-organisms have not been established in adequate and well-controlled clinical studies:

Aerobic and Facultative Anaerobic Gram-Positive Micro-organisms

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 Micro-organisms

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 Micro-organisms

Fusobacterium species.

Pharmacokinetics

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}).

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 micrograms (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.

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 paediatric patients are presented in Table 2.

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 litres (0.11 litre/kg), approximately 0.2 litre/kg in paediatric patients 3 months to 12 years of age and approximately 0.16 litre/kg in paediatric 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.

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 Interactions).

Metabolism

In healthy young adults, after IV infusion of radiolabelled 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 Interactions).

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 paediatric patients 3 months to 12 years of age.

Following administration of a 1 g radiolabelled IV dose of ertapenem to healthy young adults, approximately 80% is recovered in urine and 10% in faeces. Of the 80% recovered in urine, approximately 38% is excreted as unchanged medicine 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 post dose and exceed 52 mcg/mL during the period 12 to 24 hours post dose.

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.

Paediatric Patients

Plasma concentrations of ertapenem are comparable in paediatric 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 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

The pharmacokinetics of ertapenem in patients with hepatic insufficiency have not been established. Due to the limited extent of hepatic metabolism of ertapenem, its

pharmacokinetics are not expected to be affected by hepatic impairment. Therefore, no dosage adjustment is necessary 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 m²) 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 m²) 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 m²) 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 m²) approximately 2.9-fold compared with healthy subjects. Following a single 1 g IV dose given immediately prior to a haemodialysis session, approximately 30% of the dose is recovered in the dialysate. There are no data in paediatric patients with renal insufficiency.

A dosage adjustment is recommended for adult patients with advanced or end-stage renal insufficiency (see Dosage and Administration).

Pharmaceutical Precautions

Before reconstitution

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

Reconstituted and infusion solutions

The reconstituted solution, immediately diluted in 0.9% Sodium Chloride Injection (see Dosage and Administration, *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.

Medicine Classification

Prescription Medicine

Package Quantities

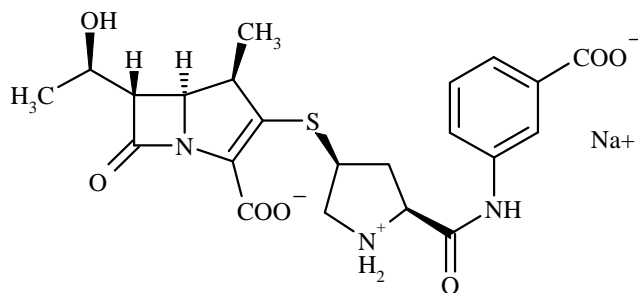
Single dose vials.

Further Information

Chemistry

INVANZ (ertapenem sodium, MSD) is chemically described as [4*R*-[3(3*S**,5*S**),4 α ,5 β ,6 β (*R**)]]-3-[[5-[[[(3-carboxyphenyl)amino]carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0] hept-2-ene-2-carboxylic acid monosodium salt.

Its empirical formula is C₂₂H₂₄N₃O₇SNa, and its structural formula is:



Composition

Active Ingredients

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

Inactive Ingredients

Each vial of INVANZ contains the following inactive ingredients: 175 mg sodium bicarbonate and sodium hydroxide to adjust pH to 7.5.

Name and Address

Merck Sharp & Dohme (NZ) Limited
P O Box 99 851
Newmarket
Auckland
NEW ZEALAND
Tel: 0800 500 673

Date of Preparation

28 June 2010

DP-IVZ-0310(280610)

®Registered Trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA

Copyright © 2008 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA All Rights Reserved