AUSTRALIAN PRODUCT INFORMATION

INVANZ®

(ertapenem sodium)
Powder for injection

1 NAME OF THE MEDICINE

Ertapenem sodium.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ertapenem sodium is a white to off-white hygroscopic, weakly crystalline powder. It is soluble in water and 0.9% sodium chloride solution, practically insoluble in ethanol, and insoluble in isopropyl acetate and tetrahydrofuran.

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

Each vial contains 1.046 g ertapenem sodium, equivalent to 1 g ertapenem.

For the full list of excipients, see **Section 6.1 List of Excipients**.

3 PHARMACEUTICAL FORM

INVANZ (ertapenem sodium) is supplied as sterile, synthetic, lyophilised powder for intravenous infusion after reconstitution with appropriate diluent (see **Section 4.2 Dose and Method of Administration**) for transfer to 50 mL 0.9% Sodium Chloride Injection or intramuscular injection following reconstitution with 1% lidocaine hydrochloride.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment
INVANZ is indicated for the treatment of patients, aged 3 months or more, with moderate to severe infections (except meningitis, see **Section 4.4 Special Warnings and Precautions for Use**) caused by susceptible strains of microorganisms which are suspected or proven to be resistant to all other antibiotics, or for patients unable to tolerate other antibiotics.

INVANZ is also indicated for initial empiric therapy for the treatment of complicated intra-abdominal infections and acute pelvic infections including post-partum endomyometritis, septic abortion and post-surgical gynaecological infections.

INVANZ is also indicated for the treatment of diabetic foot infections, which require parenteral antibiotic therapy and are caused by susceptible bacterial pathogens which are suspected or proven to be resistant to all other registered antibiotics, or for patients unable to tolerate other antibiotics.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to ertapenem. Therapy with INVANZ may be initiated empirically before the results of these tests are known; once these results become available, antimicrobial therapy should be adjusted accordingly.

4.2 DOSE AND METHOD OF 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 **Section 4.1 Therapeutic 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.

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

Patients on haemodialysis: In a clinical study in adults, 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 patients on haemodialysis are given the recommended daily dose of 500 mg of INVANZ within 6 hours prior to haemodialysis, a supplementary dose of 150mg 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 paediatric patients undergoing haemodialysis. There are no data in adult and paediatric patients undergoing peritoneal dialysis or haemofiltration.

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

Males: $\frac{\text{(weight in kg) x (140-age in years) x 1.2}}{\text{serum creatinine (micromol/L)}}$

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

No dosage adjustment is recommended in patients with impaired hepatic function (see **Section Section 5.2 Pharmacokinetic Properties, Hepatic insufficiency**).

In patients 13 years of age and older, the recommended dose of INVANZ can be administered without regard to age 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 Injections, 0.9% Sodium Chloride Injection or Bacteriostatic Water for Injections.
2. Shake well to dissolve and immediately transfer the contents of the reconstituted vial to 50 mL of 0.9% Sodium Chloride Injection. The resulting solution is chemically and physically stable only if used within 6 hours at room temperature, or stored for 24 hours at 2 to 8° C and used within 4 hours after removal from refrigeration.
3. To ensure adequate potency and to avoid microbiological hazard, the INVANZ solution should be used as soon as practicable after reconstitution and further dilution. If storage is unavoidable, the solution should be held at 2 to 8°C for not more than 24 hours, and used as soon as practicable within 4 hours after removal from refrigeration. The INVANZ solution should not be frozen.
4. INVANZ should be infused over a period of 30 minutes.

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 adrenaline (epinephrine)**). Shake vial thoroughly to form solution. This solution is chemically and physically stable for only 1 hour at 2 to 8°C.
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. To ensure adequate potency and to avoid microbiological hazard, the reconstituted solution should be used immediately or stored at 2 to 8°C for not more than 1 hour. **Note: This reconstituted solution is for intramuscular administration only. It must 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 Injections, 0.9% Sodium Chloride Injection or Bacteriostatic Water for Injections.
2. Shake well to dissolve and immediately withdraw a volume equal to 15 mg/kg of bodyweight and dilute in 0.9% Sodium Chloride Injection to a final concentration of 20 mg/mL or less. The resulting solution is chemically and physically stable only if used within 6 hours at room temperature, or stored for 24 hours at 2 to 8°C and used within 4 hours after removal from refrigeration.
3. To ensure adequate potency and to avoid microbiological hazard, the INVANZ solution should be used as soon as practicable after reconstitution and further dilution. If storage is

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

unavoidable, the solution should be held at 2 to 8°C for not more than 24 hours and used as soon as practicable within 4 hours after removal from refrigeration. The INVANZ solution should not be frozen.
4. INVANZ should be infused over a period of 30 minutes.

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 adrenaline (epinephrine)**). Shake vial thoroughly to form solution. This solution is chemically and physically stable for only 1 hour at 2 to 8°C.
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).

To ensure adequate potency and to avoid microbiological hazard, the reconstituted solution should be used immediately or stored at 2 to 8°C for not more than 1 hour. **Note: This reconstituted solution is for intramuscular administration only. It must not be administered intravenously.**

Parenteral drug 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.

Product is for single use in one patient only. Discard any residue.

4.3 CONTRAINDICATIONS

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

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

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

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

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ertapenem. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with ertapenem use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. In moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluid, electrolytes and protein replacement should be provided when indicated.

Caution should be taken when administering INVANZ intramuscularly, to avoid inadvertent injection into a blood vessel (see **Section 4.2 Dose and Method of Administration**). Lidocaine HCl is the diluent for intramuscular administration of INVANZ. Refer to the prescribing information for lidocaine HCl.

Seizure and other central nervous system (CNS) adverse experiences have been reported during treatment with INVANZ (see **Section 4.8 Adverse Effects (Undesirable Effects)**). During clinical investigations in adult patients treated with INVANZ (1 g once a day), seizures, irrespective of drug relationship, occurred in 0.5% of patients during study therapy plus 14 day follow-up period. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. Close adherence to the recommended dosage regimen is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically and the dosage of INVANZ re-examined to determine whether it should be decreased or discontinued.

Severe Cutaneous Adverse Reactions
Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected, INVANZ should be discontinued immediately and an alternative treatment should be considered.

Use in CNS infections

INVANZ is not recommended in the treatment of meningitis or other CNS infections in the paediatric population due to a lack of sufficient CSF penetration to cover all relevant pathogens.

Use in hepatic impairment

See **Section 5.2 Pharmacokinetic Properties, Hepatic insufficiency.**

Use in renal impairment

See **Section 5.2 Pharmacokinetic Properties, Renal insufficiency** and **Section 4.2 Dose and Method of Administration.**

Use in the elderly

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

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 and 2 to 17 years of age in intra abdominal infection (IAI) and acute pelvic infection (API)* comparator-controlled studies (see **Section 4.1 Therapeutic Indications** and **Section 5.1 Pharmacodynamic Properties, Clinical trials, Paediatric patients**). There are no data in paediatric patients with renal insufficiency.

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

Effects on laboratory tests

See **Section 4.8 Adverse Effects (Undesirable Effects), Laboratory tests.**

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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 AUC (25%). No dosage adjustment is necessary when ertapenem is given with probenecid. Because of the small effect on half-life, the co-administration with probenecid to extend the half-life of ertapenem is not recommended.

In vitro studies indicate that ertapenem does not inhibit P-glycoprotein-mediated transport of digoxin or vinblastine and that ertapenem is not a substrate for P-glycoprotein-mediated transport. *In vitro* studies in human liver microsomes indicate ertapenem does not inhibit metabolism mediated by any of the six major cytochrome p450 (CYP) isoforms: 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. Drug interactions caused by inhibition of P-glycoprotein-mediated drug clearance or CYP-mediated drug clearance are unlikely (see **Section 5.2 Pharmacokinetic Properties, Distribution and Metabolism**.)

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

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.

Case reports in the literature have shown that co-administration of carbapenems, including ertapenem, to patients receiving valproic acid or divalproex sodium results in a reduction of valproic acid concentrations. The valproic acid concentrations may drop below the therapeutic range as a result of this interaction, therefore increasing the risk of breakthrough seizures. Increasing the dose of valproic acid or divalproex sodium may not be sufficient to overcome this interaction. Although the mechanism of this interaction is unknown, data from *in vitro* and animal studies suggest that carbapenems may inhibit the hydrolysis of valproic acid's glucuronide metabolite (VPA-g) back to valproic acid, thus decreasing the serum concentrations of valproic acid.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Ertapenem had no adverse effect on fertility of either male or female rats at doses up to 700 mg/kg/day IV, which was associated with a plasma AUC level similar to the anticipated human value at the clinically recommended dose.

* Acute pelvic infection is not the same entity as pelvic inflammatory disease

Use in pregnancy

(Category B3)

In mice and rats given IV doses of up to 700 mg/kg/day (for rats, similar to human exposure at the recommended dose of 1 g based on plasma AUCs; no exposure data were available for mice), there was no evidence of developmental toxicity as assessed by external, visceral, and skeletal examination of the fetuses. However, in mice given 700 mg/kg/day, slight decreases in average fetal weights and an associated decrease in the average number of ossified sacrocaudal vertebrae were observed. Ertapenem crosses the placental barrier in rats.

There are no adequate and well-controlled studies in pregnant women. INVANZ should not be used in pregnant women, unless the expected therapeutic benefit to the mother clearly outweighs the potential risk to the mother and fetus.

Use in lactation

Ertapenem is excreted in human milk (see **Section 5.2 Pharmacokinetic Properties, Distribution**). In rats given IV doses of up to 700 mg/kg/day (similar to human exposure at the recommended dose of 1 g based on plasma AUCs) there was no evidence of post-natal toxicity. INVANZ should not be used in a breastfeeding woman, unless the expected therapeutic benefit to the mother clearly outweighs the potential risk to the infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Dizziness and somnolence can occur which may affect some patients' ability to drive and/or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

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

The following drug-related adverse experiences were reported during parenteral therapy in ≥1.0% of patients treated with ertapenem:

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

Adverse Events	Ertapenem 1 g daily (N=1866)	Piperacillin/ Tazobactam 3.375 g q6h (N=775)	Ceftriaxone 1 or 2 g daily (N=912)
Local:			
Infused vein complication	3.9	5.5	4.3
Phlebitis/thrombophlebitis	1.3	1.3	1.4
Systemic:			
Diarrhoea	4.3	6.6	3.7

Nausea	2.9	3.2	2.6
Headache	2.1	1.0	2.2
Vomiting	1.0	1.5	0.9
*Determined by the investigator to be possibly, probably, or definitely drug-related			

Additional drug-related adverse experiences that were reported during parenteral therapy with ertapenem with an incidence > 0.1% but < 1.0% within each body system are listed below:

Body as a whole: asthenia/fatigue, candidiasis, oedema/swelling, fever, pain, abdominal pain, chest pain;
Cardiovascular System: extravasation, hypotension, bradycardia;
Digestive System: acid regurgitation, anorexia, oral candidiasis, constipation, *C. difficile*-associated diarrhoea, dry mouth, dyspepsia;
Nervous System & Psychiatric: confusion, dizziness, insomnia, somnolence;
Respiratory System: dyspnoea;
Skin & Skin Appendage: *e*rythema, pruritus;
Special Senses: taste perversion;
Urogenital System: vaginal pruritus.

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

In the majority of clinical studies, parenteral therapy was followed by a switch to an appropriate oral antimicrobial (see **Section 5.1 Pharmacodynamic Properties, Clinical trials**). During the entire treatment period and a 14 day post-treatment follow-up period, drug-related adverse experiences in patients treated with ertapenem included those listed above as well as rash and vaginitis at an incidence of ≥1.0% (common) and allergic reactions, malaise and fungal infections at an incidence of >0.1 % but <1.0% (uncommon).

In a clinical study for the treatment of diabetic foot infections in which 289 adult diabetic patients were treated with ertapenem, the drug related adverse experience profile was generally similar to that seen in previous clinical trials.

Paediatric patients
Clinical studies enrolled 384 paediatric patients treated with ertapenem. The overall adverse experience profile is comparable to that in adult patients. Table 2 shows the incidence of drug-related adverse experiences reported during parenteral therapy in ≥1.0% of paediatric patients in these studies.

Table 2
Incidence (%) of Drug-Related Adverse Experiences* Reported During Parenteral Therapy in ≥1.0% of Paediatric Patients Treated with Ertapenem in Clinical Studies

Adverse Events	Ertapenem (N=384)	Ceftriaxone (N=100)	Ticarcillin/clavulanate (N=24)
Local:			
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
Systemic:			

Diarrhea	5.5	10.0	4.2
Rash	1.3	1.0	4.2
Vomiting	1.6	2.0	0.0
*Determined by the investigator to be possibly, probably, or definitely drug-related			

In the paediatric clinical studies, the majority of the patients had parenteral therapy followed by a switch to an appropriate oral antimicrobial (see **Section 5.1 Pharmacodynamic Properties, Clinical trials**). During the entire treatment period and a 14 day posttreatment follow-up period, drug-related adverse experiences reported with an incidence of ≥1.0% in patients treated with ertapenem were no different than those listed in Table 2.

Additional drug-related adverse experiences that were reported during parenteral therapy with ertapenem with an incidence >0.5% but <1.0% within each body system are listed below:

General disorders and administration site conditions: infusion site induration, infusion site pruritus, infusion site warmth
Vascular disorders: phlebitis

Post-Marketing Experience
The following post-marketing adverse experiences have been reported:
Immune System: anaphylaxis including anaphylactoid reactions
Psychiatric Disorders: altered mental status (including agitation, aggression, delirium, disorientation, mental status changes)
Nervous System Disorders: depressed level of consciousness, dyskinesia, gait disturbance, hallucinations, myoclonus, tremor, encephalopathy (recovery may be prolonged in patients with renal impairment). Seizures (very rare). Seizures occurred most frequently in elderly patients and those with pre-existing CNS disorders (e.g. brain lesions or history of seizures) and/or compromised renal function (see **Section 4.4 Special Warnings and Precautions for Use**).
Gastrointestinal Disorders: teeth staining
*Skin and Other Subcutaneous Tissue Disorders: S*evere cutaneous adverse reactions (SCAR), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported with beta-lactam antibiotics; urticaria, hypersensitivity vasculitis
Musculoskeletal and Connective Tissue Disorders: muscular weakness

Laboratory Tests

Adult Patients
Clinically Significant Laboratory Abnormalities that were measured during parenteral therapy in ≥1.0% of patients treated with ertapenem in clinical studies are presented in Table 3.

Table 3
Incidence (%) of Clinically Significant Laboratory Abnormalities (CLSA) Reported During Parenteral Therapy in ≥1.0% of Patients Treated with Ertapenem in Clinical Studies

Laboratory Test (CLSA Criteria)	Ertapenem 1 g daily ($n^{†‡}$=1866)	Piperacillin/ Tazobactam 3.375 g q6h ($n^{†}$=775)	Ceftriaxone 1 or 2 g daily ($n^{‡§}$=912)
Absolute Neutrophil Count (<1,800 cells/µL)	3.0	1.4	1.9
ALT (>2.5xULN)	4.8	3.0	5.7

AST (>2.5xULN)	5.5	4.5	4.2
Direct Serum Bilirubin (>2.5xULN)	3.2	4.3	0.8
Haematocrit (<24%)	2.7	3.5	1.4
Haemoglobin (<8g/dL)	3.1	3.8	0.9
Platelet Count (<75,000 cells/µL)	1.2	1.0	1.1
Serum Alkaline Phosphatase (>2.5xULN)	2.4	2.6	1.7
Serum Creatinine (>1.5xULN)	1.3	2.8	1.5
Total Serum Bilirubin (>2.5xULN)	1.1	1.2	0.4
† Includes adult patients with renal dose adjustments. ‡ Includes adult patients randomised to 1 g but dose adjusted to 2 g. § Includes adult patients who also received metronidazole. N = The total number of treated patients in the treatment group. ULN = Upper limit of normal range			

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

In the majority of clinical studies, parenteral therapy was followed by a switch to an appropriate oral antimicrobial (see **Section 5.1 Pharmacodynamic Properties, Clinical trials**). During the entire treatment period and a 14 day post-treatment follow-up period, drug-related laboratory abnormalities in patients treated with ertapenem were no different than those listed above.

Other drug-related laboratory abnormalities included the following: increases in direct serum bilirubin, total serum bilirubin, eosinophils, indirect serum bilirubin, PTT, urine bacteria, BUN, serum creatinine, serum glucose, monocytes, urine epithelial cells, urine red blood cells; decreases in segmented neutrophils, white blood cells, 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 drug-related laboratory adverse experience profile was generally similar to that seen with previous clinical trials.

Paediatric Patients
The overall laboratory adverse experience profile is comparable to that in adults. Table 4 shows the incidence of laboratory adverse experiences reported in ≥1.0% of paediatric patients in clinical studies.

Table 4
Incidence* (%) of Specific Drug-Related Laboratory Adverse Experiences Reported During Parenteral Therapy in ≥1.0% of Paediatric Patients Treated with Ertapenem in Clinical Studies

Laboratory adverse experiences	Ertapenem N†=384	Ceftriaxone (N†=100)	Ticarcillin/ clavulanate (N†=24)
ALT ↑	1.9	0.0	4.3
AST ↑	1.9	0.0	4.3

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 paediatric patients treated with ertapenem in clinical studies include: increase in eosinophils.

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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 overdosage.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pharmacotherapeutic Group: Carbapenem, ATC code: J01D HXX

Microbiology

Ertapenem has *in vitro* activity against a wide range of gram-positive and gram-negative aerobic and anaerobic bacteria. The bactericidal activity of ertapenem results from the inhibition of cell wall synthesis and is mediated through ertapenem binding to penicillin binding proteins (PBPs). In *Escherichia coli,* it has strong affinity toward PBPs 1a, 1b, 2, 3, 4 and 5 with preference for PBPs 2 and 3. Ertapenem has significant stability against hydrolysis by most classes of beta-lactamases, including penicillinases, and cephalosporinases and extended spectrum beta-lactamases, but not metallo-beta-lactamases.

Ertapenem has been shown to be active against most strains of the following microorganisms *in vitro* and in clinical infections:

AEROBIC AND FACULTATIVE ANAEROBIC GRAM-POSITIVE MICROORGANISMS:

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

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

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

The following *in vitro* data are available, **but their clinical significance is unknown.**

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

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

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

ANAEROBIC MICROORGANISMS:
Fusobacterium species.

Clinical trials†

Adult Patients

Complicated Intra-Abdominal Infections

Ertapenem was evaluated in adults for the treatment of complicated intra-abdominal infections in a randomised, multicentre, double-blind, controlled clinical trial. This study compared ertapenem (1 g IV once a day) with piperacillin/tazobactam (3.375 g IV every 6 hours) for 5 to 14 days and enrolled 665 patients. In this study, complicated intra-abdominal infections were defined as those requiring surgical intervention and which extend beyond the hollow viscus into the peritoneal space. Patients were stratified at baseline into two groups: localised complicated appendicitis (stratum 1) and any other complicated intra-abdominal infection including colonic, small intestinal, and biliary infections and generalised peritonitis (stratum 2). At 1 to 2 weeks post-therapy, the clinical and microbiological success rates were 89.6% (190/212) for ertapenem and 82.7% (162/196) for piperacillin/tazobactam; at 4 to 6 weeks post-therapy (test of cure) success rates were 86.7% (176/203) for ertapenem and 81.3% (157/193) for piperacillin/tazobactam. At the test of cure for patients in stratum 1 the success rates were 90.4% (85/94) for ertapenem and 90.1% (82/91) for piperacillin/tazobactam, and for patients in stratum 2 the success rates were 83.5% (91/109) for ertapenem and 73.5% (75/102) for piperacillin/tazobactam. The clinical success rates at the test of cure by pathogen in the microbiologically evaluable patients are presented in Table 5.

Table 5
Clinical Success Rates at the Test of Cure by Pathogen for Microbiologically Evaluable Adult Patients with Complicated Intra-Abdominal Infections

Pathogen	**Ertapenem % (n/N)***	**Piperacillin/Tazobactam % (n/N)***
Escherichia coli	86.7 (137/158)	80.0 (108/135)
Klebsiella pneumoniae	92.9 (13/14)	70.6 (12/17)
Clostridia species	88.8 (71/80)	78.1 (50/64)
Eubacterium species	92.7 (38/41)	86.2 (25/29)
Peptostreptococcus species	80.6 (29/36)	88.5 (23/26)
Bacteroides fragilis group†	86.7 (183/211)	85.9 (177/206)
Prevotella species	80.0 (20/25)	76.5 (13/17)

* Number of isolates with favourable response assessment/Total number of isolates
† Includes *Bacteroides fragilis* and species in the *B. fragilis* group

In patients with *E. coli* bacteraemia, 100% (3/3) were treated successfully with ertapenem.

Acute Pelvic Infections including postpartum endomyometritis, septic abortion and postsurgical gynaecologic infections

Ertapenem was evaluated in adults for the treatment of acute pelvic infections in a randomised, multicentre, double-blind, controlled clinical trial. This study compared ertapenem (1 g IV once a day) with piperacillin/tazobactam (3.375 g IV every 6 hours) for 3 to 10 days and enrolled 412 patients including 350 patients with obstetric/postpartum infections and 45 patients with septic abortion. The clinical success rates at 2 to 4 weeks post-therapy

† Reported cure rates are based on assessable subjects (excludes indeterminate and missing values)

(test of cure) were 93.9% (153/163) for ertapenem and 91.5% (140/153) for piperacillin/tazobactam. The clinical success rates at the test of cure by pathogen in the microbiologically evaluable patients are presented in Table 6.

Table 6
Clinical Success Rates at the Test of Cure by Pathogen for Microbiologically Evaluable Adult Patients with Acute Pelvic Infections

Pathogen	Ertapenem % (n/N)*	Piperacillin/Tazobactam % (n/N)*
Streptococcus agalactiae	90.9 (10/11)	93.8 (15/16)
Escherichia coli	87.8 (36/41)	92.3 (36/39)
Clostridia species	100 (11/11)	100 (10/10)
Peptostreptococcus species	96.4 (80/83)	92.7 (76/82)
Bacteroides fragilis group†	96.8 (30/31)	92.5 (37/40)
Porphyromonas asaccharolytica	92.9 (13/14)	92.3 (12/13)
Prevotella species	96.3 (52/54)	92.0 (46/50)

* Number of isolates with favourable response assessment/Total number of isolates

† Includes *Bacteroides fragilis* and species in the *B. fragilis* group

In patients with *E. coli* bacteraemia, 100% (6/6) were treated successfully with ertapenem.

Bacterial Septicaemia

In a composite analysis of data from pivotal and supportive studies 172 evaluable patients were bacteremic. Overall, 69/86 (80.2%) patients in the ertapenem group and 72/86 (83.7%) patients in the combined ceftriaxone and piperacillin/tazobactam groups had a favourable response assessment (test of cure). The primary efficacy response rates at the test of cure by pathogen in the evaluable patients are presented in Table 7.

Table 7
Primary Efficacy Response Rates at the Test of Cure by Pathogen (for Those Pathogens Identified ≥5 Times in One or More Treatment Groups) for Evaluable Patients with Bacterial Septicaemia

Indication	Pathogen	Ertapenem % (n/N)*	Piperacillin / Tazobactam % (n/N)*
Complicated intra-abdominal infections and acute pelvic infections	*Escherichia coli*	100 (9/9)	80.0 (4/5)
Overall ertapenem vs piperacillin/tazobactam	*Staphylococcus aureus*	40.0 (2/5)	60.0 (3/5)
	Escherichia coli	100 (9/9)	83.3 (5/6)

* Number of pathogens with associated favourable primary efficacy assessment/number of pathogens with an assessment

Diabetic Foot Infections

Ertapenem was evaluated in adults for the treatment of diabetic foot infections in a randomized, multicenter, double-blind, controlled clinical trial. This study compared ertapenem (1 g IV once a day) with piperacillin/tazobactam (3.375 g IV every 6 hours) and enrolled 586 patients. Both regimens allowed the option to switch to oral amoxicillin/clavulanate for a total of 5 to 28 days of treatment (parenteral and oral). Adults

with Type I or Type II diabetes with moderate to severe diabetic foot infections requiring parenteral antibiotic therapy were enrolled. Subjects with suspected osteomyelitis were excluded. Efficacy analyses took into consideration the investigator's assessment of the severity of the baseline wound. For the primary analysis, 94.2% of patients in the ertapenem group and 92.2% of patients in the piperacillin/tazobactam group had a favourable response assessment at the discontinuation of IV therapy assessment (DCIV) visit. The clinical success rates at 10 days posttherapy were 87.4% (180/206) for ertapenem and 82.7% (162/196) for piperacillin/tazobactam. The clinical success rates for both the DCIV assessment and 10 day post treatment follow up assessment (FUA) are presented in Table 8a.

Table 8a.
Favourable response assessment at DCIV and FUA visits (estimated)

Response assessed		Ertapenem (A)		Piperacillin/Tazobactam (B)		Estimated difference (A-B)	CR
		N	% (95 CI)	N	% (95 CI)	5 (95% CI)	%
Discontinuation of IV Therapy Assessment (DCIV)							
Clinical	EPP*	226	94.2 (91.1; 97.2)	219	92.2 (88.7; 95.8)	1.9 (-2.9; 6.9)	-15
10 Day post-treatment Follow-up Assessment(FUA)							
Clinical	EPP**	206	87.4 (82.8; 91.9)	196	82.7 (77.5; 87.9)	4.7 (-2.2; 11.9)	-15

Computed from statistical model adjusting for severity data.
CR = lower limit of the confidence interval required for equivalence
* primary hypothesis
** secondary hypothesis
N = number of evaluable patients in each treatment group
CI = confidence interval
EPP = evaluable per protocol

The clinical success rates at the posttherapy visit by pathogen in the clinically evaluable patients are presented in Table 8b.

Table 8b.
Clinical Success Rates at the Posttherapy Visit by Pathogen for Clinically Evaluable Adult Patients with Diabetic Foot Infections

Pathogen	**Ertapenem % (n/N)***	**Piperacillin/Tazobactam % (n/N)***
Staphylococcus aureus (MSSA)	84.5 (60/71)	81.3 (52/64)
Streptococcus	100.0 (11/11)	83.3 (5/6)
Streptococcus agalactiae	71.4 (15/21)	84.6 (22/26)
Escherichia coli	90.9 (10/11)	100.0 (5/5)
Peptostreptococcus species	91.8 (56/61)	81.1 (43/53)
Porphyromonas asaccharolytica	60.0 (6/10)	71.4 (5/7)
Prevotella species	87.0 (20/23)	78.9 (15/19)
Bacteroides fragilis group†	90.0 (18/20)	72.9 (10/13)

* Number of isolates with favourable response assessment/Total number of isolates
† Includes *Bacteroides fragilis* and species in the *B. fragilis* group

Paediatric Patients

Ertapenem was evaluated in paediatric patients in a study which enrolled 112 patients and compared ertapenem (15 mg/kg IV every 12 hours in patients 2 to 12 years of age, and 1 g IV once a day in patients 13 to 17 years of age) to ticarcillin/clavulanate (50 mg/kg for patients <60 kg or 3.0 g for patients >60 kg, 4 or 6 times a day) up to 14 days for the treatment of complicated intra-abdominal infections (IAI) and acute pelvic infections (API). The response rates for the EPP population are presented in Table 9.

Paediatric experience in intra abdominal infections (IAI) and acute pelvic infections (API) is limited to children 2 years and older, and bacterial septicaemia has not been studied in this population.

Table 9.
Efficacy at post-treatment follow-up assessment: proportion of patients with a favourable clinical response assessment at the EPP test of cure visit displayed by disease stratum

Disease Stratum	**Ertapenem % (n/m)***	**Ticarcillin/Clavulanate % (n/m)***
Complicated Intra Abdominal Infections	83.7 (36/43)	63.6 (7/11)
Acute Pelvic Infections	100 (23/23)	100 (4/4)
* Number of patients with a favourable assessment/ number of patients in clinical EPP population		

A second study assessing the effect of ertapenem in additional infections not approved in adults included paediatric patients, recruitment criteria age range, 3 months to 17 years of age. This study enrolled 404 patients and compared ertapenem (15 mg/kg IV every 12 hours in patients 3 months to 12 years of age, and 1 g IV once a day in patients 13 to 17 years of age) to ceftriaxone (50 mg/kg/day IV in two divided doses in patients 3 months to 12 years of age and 50 mg/kg/day IV as a single daily dose in patients 13 to 17 years of age) for the treatment of complicated urinary tract infection (UTI), skin and soft tissue infection (SSTI), or community- acquired pneumonia (CAP). Both regimens allowed the option to switch to oral amoxicillin/clavulanate for a total of up to 14 days of treatment (parenteral and oral).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Ertapenem, reconstituted with 1% lidocaine HCl injection, USP (in saline without adrenaline (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}).

Average plasma concentrations (µg/mL) of ertapenem following a single 30-minute IV infusion of a 1 g dose and IM administration of a single 1 g dose in healthy young adults are presented in Table 10.

Table 10 **Plasma Concentrations of Ertapenem After Single Dose Administration**									
Dose/Route	Average Plasma Concentrations (µg/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
*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 (µg/mL) of ertapenem in paediatric patients are presented in Table 11.

Table 11 **Plasma Concentrations of Ertapenem in Paediatric 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 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								

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 µg/mL to approximately 85% bound at an approximate plasma concentration of 300 µg/mL.

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 12. The ratio of AUC in skin blister fluid to AUC in plasma is 0.61.

Table 12
Concentrations (µg/mL) of Ertapenem in Adult Skin Blister Fluid at Each Sampling Point on the Third Day of 1 g Once Daily IV Doses

0.5 hr	1 hr	2 hr	4 hr	8 hr	12 hr	24 hr
7	12	17	24	24	21	8

The level of ertapenem in breast milk of 5 lactating women was measured at random time points daily for 5 consecutive days following the last 1 g dose of intravenous therapy. The measured concentration of ertapenem in breast milk on the last day of therapy (5 to 14 days postpartum) in all 5 women was < 0.38 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 **Section 4.5 Interactions with Other Medicines and Other Forms of 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 **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**).

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 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 drug and approximately 37% as the ring-opened metabolite.

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

Gender

Following administration of a 1 g IV dose over 30 minutes, the plasma concentrations (AUC) of ertapenem, both total and unbound, were similar in healthy male and female subjects (total drug AUC was 570.0 µg.hr/mL for men vs 566.8 µg.hr/mL for women).

Elderly

Following a 1 g IV dose of ertapenem, AUC increases by approximately 39% in elderly subjects (≥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 **5.2 Pharmacokinetic Properties, 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 m^2) compared with healthy subjects (ages 25 to 82 years). AUC is increased in patients with moderate renal insufficiency (Cl_{Cr} 31-59 mL/min/1.73 m^2) approximately 1.5-fold compared with healthy subjects. AUC is increased in patients with advanced renal insufficiency (Cl_{Cr} 5-30 mL/min/1.73 m^2) approximately 2.6-fold compared with healthy subjects. AUC is increased in patients with end-stage renal insufficiency (Cl_{Cr} <10 mL/min/1.73 m^2) approximately 2.9-fold compared with healthy subjects. Following a single 1 g IV dose given immediately prior to a 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 **Section 4.2 Dose and Method of Administration**).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Ertapenem was not genotoxic, as assessed *in vitro* for gene mutations, chromosomal aberrations and DNA strand breaks in cultured mammalian cells. An *in vivo* assay of chromosomal damage (micronucleus test in mice) was also negative.

Carcinogenicity

The carcinogenic potential of ertapenem has not been examined in long-term animal studies.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each vial contains the inactive ingredients sodium bicarbonate and sodium hydroxide. The sodium content is approximately 137 mg (approximately 6.0 mEq).

6.2 INCOMPATIBILITIES

See **Section 4.2 Dose and Method of Administration, Instructions for Use.**

6.3 SHELF LIFE

Before reconstitution, INVANZ has a shelf-life of 24 months when stored below 25°C

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Before reconstitution
Store lyophilised powder below 25°C.

Reconstituted and infusion solutions
For storage instructions for the reconstituted injection, see **Section 4.2 Dose and Method of Administration, Instructions for Use**.

6.5 NATURE AND CONTENTS OF CONTAINER

INVANZ is supplied as sterile lyophilized powder for intravenous infusion after reconstitution with appropriate diluent (see **Section 4.2 Dose and Method of Administration, Instructions for Use**) for transfer to 50 mL 0.9% sodium chloride injection or for intramuscular injection following reconstitution with 1% lidocaine hydrochloride. Each vial contains 1.046 g ertapenem sodium, equivalent to 1 g ertapenem.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

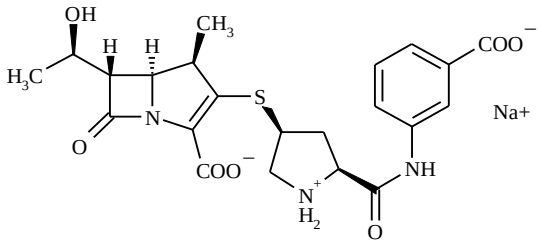
6.7 PHYSICOCHEMICAL PROPERTIES

INVANZ (ertapenem sodium) powder for Injection is a sterile, synthetic, parenteral, 1-β methyl-carbapenem that is structurally related to beta-lactam antibiotics, such as penicillins and cephalosporins.

INVANZ (ertapenem sodium) is chemically described as [4*R*-[3(3*S**,5*S**), 4α, 5β, 6β *(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 $C_{22}H_{24}N_3O_7SNa$ and its molecular weight is 497.50.

Chemical structure



CAS number

153832-38-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

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6 September 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
N/A	Revised Copyright statement. Minor editorial and formatting revisions were made throughout the document
	Lidocaine (lignocaine) dual labelling revised single labelling only

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