NEW ZEALAND DATA SHEET

1 PRODUCT NAME

INVANZ (ertapenem sodium) 1 g Powder for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect: Sodium.

Each 1.0 g dose contains approximately 6.0 mEq of sodium (approximately 137 mg).

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

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Dose and method of administration

Dose

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).

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.

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.

Special populations

Paediatric population

The safety and efficacy of INVANZ in children below 3 months of age have not been established.

Elderly

The recommended dose of INVANZ should be administered except in cases of severe renal impairment (see Renal impairment).

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

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

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

Method of administration

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.

For instructions on reconstitution of the medicine before administration, see **Section 6.6 Special precautions for disposal and other handling**.

4.3 Contraindications

INVANZ is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients listed in **Section 6.1 List of excipients** 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.)

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 medicine immediately. **Serious anaphylactic reactions require immediate emergency treatment.**

Seizures and other central nervous system (CNS) adverse experiences have been reported during treatment with INVANZ (see **Section 4.8 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.

The concomitant use of INVANZ and valproic acid/divalproex sodium is not recommended (see **Section 4.5 Interactions with other medicines and other forms of 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 **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.

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.

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 **Section 4.2 Dose and method of administration**.)

Paediatric population

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 **Section 4.1 Therapeutic 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.

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 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 **Section 5.2 Pharmacokinetic properties**, **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 valproic acid or divalproex sodium 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 valproic acid or divalproex sodium 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.

4.6 Fertility, pregnancy and lactation

Pregnancy (Category B3)

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.

Breast-feeding

Ertapenem is excreted in human milk (see Section 5.2 Pharmacokinetic properties**,** Distribution**). Caution should be exercised when INVANZ is administered to a nursing woman.**

Fertility

See **Section 5.3 Preclinical safety data, Animal Toxicology, Reproduction.**

4.7 Effects on ability to drive and use machines

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

4.8 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. 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 (≥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 ≥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 (≥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: decreased level of consciousness, dyskinesia, gait disturbance, hallucinations, myoclonus, tremor, encephalopathy (recovery may be prolonged in patients with renal impairment)

Gastrointestinal Disorders: teeth staining

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

Musculoskeletal and Connective Tissue Disorders: muscular weakness

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at https://nzphvc.otago.ac.nz/reporting/.

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use

Carbapenems, ATC code: J01DH03.

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.

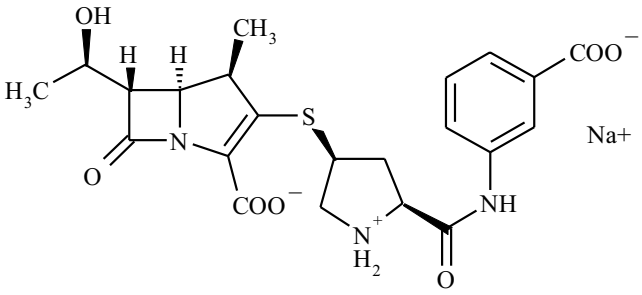
Mechanism of action

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

Chemistry

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 structural formula is:



5.2 Pharmacokinetic properties

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 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 30minute IV infusion of a 1 or 2 g dose and IM administration of a single 1 g dose in healthy young adults are presented in Table 1.

TABLE 1

Plasma Concentrations of Ertapenem in Adults After Single Dose Administration

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

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

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

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

TABLE 2

Plasma Concentrations of Ertapenem in Paediatric Patients After Single IV* Dose Administration

Age Group (Dose)	Average Plasma Concentrations (mcg/mL)							
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	24 hr
3 to 23 months								
(15 mg/kg)†	103.8	57.3	43.6	23.7	13.5	8.2	2.5	-
(20 mg/kg)†	126.8	87.6	58.7	28.4	-	12.0	3.4	0.4

(40 mg/kg)‡	199.1	144.1	95.7	58.0	-	20.2	7.7	0.6
2 to 12 years								
(15 mg/kg)†	113.2	63.9	42.1	21.9	12.8	7.6	3.0	-
(20 mg/kg)†	147.6	97.6	63.2	34.5	-	12.3	4.9	0.5
(40 mg/kg)‡	241.7	152.7	96.3	55.6	-	18.8	7.2	0.6
13 to 17 years								
(20 mg/kg)†	170.4	98.3	67.8	40.4	-	16.0	7.0	1.1
(1 g)§	155.9	110.9	74.8	-	24.0	-	6.2	-
(40 mg/kg)‡	255.0	188.7	127.9	76.2	-	31.0	15.3	2.1

* IV doses were infused at a constant rate over 30 minutes
† up to a maximum dose of 1 g/day
‡ up to a maximum dose of 2 g/day
§ Based on three patients receiving 1 g ertapenem who volunteered for pharmacokinetic assessment in one of the two safety and efficacy studies

The volume of distribution (Vdss) 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.

TABLE 3

Concentrations (mcg/mL) of Ertapenem in Adult Skin Blister Fluid at each Sampling Point on the Third Day of 1-g Once Daily IV Doses

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

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

In vitro studies indicate that ertapenem does not inhibit P-glycoprotein-mediated transport of digoxin or vinblastine and that ertapenem is not a substrate for P-glycoprotein-mediated transport (see **Section 4.5 Interactions with other medicines and other forms of interactions**).

Biotransformation

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**).

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 **Section 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**).

Antibiotic specific information

INVANZ has been shown to be active against most strains of the following micro-organisms *in vitro* and in clinical infections (see **Section 4.1 Therapeutic 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 (≥90%) strains of *Streptococcus* species including *Streptococcus pneumoniae*, ≤0.5 mcg/mL against most (≥90%) strains of *Haemophilus* species and ≤2 mcg/mL against most (≥90%) strains of the other aerobic and facultative anaerobic micro-organisms and ≤4 mcg/mL against most (≥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

5.3 Preclinical safety data

Animal Toxicology

Acute Toxicology
The approximate LD_{50} 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in **Section 6.6 Special precautions for disposal and other handling**.

6.3 Shelf life

The powder for injection has a 24 month shelf-life.

Reconstituted and infusion solutions

The reconstituted solution, immediately diluted in 0.9% Sodium Chloride Injection (see **Section 6.6 Special precautions for disposal and other handling**, **Instructions for Use**), may be stored at or below 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.

6.4 Special precautions for storage

Before reconstitution

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

For storage conditions after reconstitution of the medicine, see **Section 6.3 Shelf life**.

6.5 Nature and contents of container

Single dose glass vials.

6.6 Special precautions for disposal and other handling

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.

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.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

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

9 DATE OF FIRST APPROVAL

25 October, 2001

10 DATE OF REVISION

15 August 2023

*** Refer to the prescribing information for lidocaine HCl

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4, 4.5	Replaced sodium valproate with valproic acid, and inclusion of divalproex sodium interaction
N/A	Revised Copyright statement. Minor editorial and formatting revisions were made throughout the document.

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