SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

INVANZ 1 g powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1.0 g ertapenem.

Excipient(s) with known effect

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.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
White to yellowish off-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment

INVANZ is indicated in paediatric patients (3 months to 17 years of age) and in adults for the treatment of the following infections when caused by bacteria known or very likely to be susceptible to ertapenem and when parenteral therapy is required (see sections 4.4 and 5.1):

- Intra-abdominal infections
- Community acquired pneumonia
- Acute gynaecological infections
- Diabetic foot infections of the skin and soft tissue (see section 4.4)

Prevention

INVANZ is indicated in adults for the prophylaxis of surgical site infection following elective colorectal surgery (see section 4.4).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Treatment

Adults and adolescents (13 to 17 years of age): The dose of INVANZ is 1 gram (g) given once a day by the intravenous route (see section 6.6).

Infants and children (3 months to 12 years of age): The dose of INVANZ is 15 mg/kg given twice daily (not to exceed 1 g/day) by the intravenous route (see section 6.6).

Prevention

Adults: To prevent surgical site infections following elective colorectal surgery, the recommended dosage is 1 g administered as a single intravenous dose to be completed within 1 hour prior to the surgical incision.

Paediatric population

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

No data are available.

Renal impairment

INVANZ may be used for the treatment of infections in adult patients with mild to moderate renal impairment. In patients whose creatinine clearance is 30 mL/min/1.73 m2, no dosage adjustment is necessary. There are inadequate data on the safety and efficacy of ertapenem in patients with severe renal impairment to support a dose recommendation. Therefore, ertapenem should not be used in these patients (see section 5.2). There are no data in children and adolescents with renal impairment.

Haemodialysis

There are inadequate data on the safety and efficacy of ertapenem in patients on haemodialysis to support a dose recommendation. Therefore, ertapenem should not be used in these patients.

Hepatic impairment

No dosage adjustment is recommended in patients with impaired hepatic function (see section 5.2).

Elderly

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

Method of administration

Intravenous administration: INVANZ should be infused over a period of 30 minutes.

The usual duration of therapy with INVANZ is 3 to 14 days but may vary depending on the type and severity of infection and causative pathogen(s). When clinically indicated, a switch to an appropriate oral antibacterial agent may be implemented if clinical improvement has been observed.

For instructions on preparation of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hypersensitivity to any other carbapenem antibacterial agent.
- Severe hypersensitivity (e.g., anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g., penicillins or cephalosporins).

4.4 Special warnings and precautions for use

Hypersensitivity
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. Before initiating therapy with ertapenem, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactams and other allergens (see section 4.3). If an allergic reaction to ertapenem occurs (see section 4.8), discontinue the therapy immediately. **Serious anaphylactic reactions require immediate emergency treatment.**

Superinfection
Prolonged use of ertapenem 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.

Antibiotic-associated colitis
Antibiotic-associated colitis and pseudomembranous colitis have been reported with 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. Discontinuation of therapy with INVANZ and the administration of specific treatment for *Clostridioides difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Seizures
Seizures have been reported during clinical investigation in adult patients treated with ertapenem (1 g once a day) during therapy or in the 14-day follow-up period. Seizures occurred most commonly in elderly patients and those with pre-existing central nervous system (CNS) disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. Similar observations have been made in the post-marketing environment.

Encephalopathy
Encephalopathy has been reported with the use of ertapenem (see section 4.8). If ertapenem-induced encephalopathy is suspected (e.g., myoclonus, seizures, altered mental status, depressed level of consciousness), discontinuation of ertapenem should be considered. Patients with renal impairment are at higher risk of ertapenem-induced encephalopathy and the resolution may be prolonged.

Concomitant use with valproic acid
The concomitant use of ertapenem and valproic acid/sodium valproate is not recommended (see section 4.5).

Sub-optimal exposure
Based on the data available it cannot be excluded that in the few cases of surgical interventions exceeding 4 hours, patients could be exposed to sub-optimal ertapenem concentrations and consequently to a risk of potential treatment failure. Therefore, caution should be exercised in such unusual cases.

Considerations for use in particular populations
Experience in the use of ertapenem in the treatment of severe infections is limited. In clinical studies for the treatment of community-acquired pneumonia, in adults, 25 % of evaluable patients treated with ertapenem had severe disease (defined as pneumonia severity index > III). In a clinical study for the treatment of acute gynaecologic infections, in adults, 26 % of evaluable patients treated with ertapenem had severe disease (defined as temperature ≥ 39 °C and/or bacteraemia); ten patients had bacteraemia. Of evaluable patients treated with ertapenem in a clinical study for the treatment of intra-abdominal infections, in adults, 30 % had generalised peritonitis and 39 % had infections involving sites other than the appendix including the stomach, duodenum, small bowel, colon, and gallbladder; there were limited numbers of evaluable patients who were enrolled with APACHE II scores ≥ 15 and efficacy in these patients has not been established.

The efficacy of INVANZ in the treatment of community acquired pneumonia due to penicillin-resistant *Streptococcus pneumoniae* has not been established.

Efficacy of ertapenem in the treatment of diabetic foot infections with concurrent osteomyelitis has not been established.

There is relatively little experience with ertapenem in children less than two years of age. In this age group, particular care should be taken to establish the susceptibility of the infecting organism(s) to ertapenem. No data are available in children under 3 months of age.

Sodium
This medicinal product contains approximately 137 mg sodium per 1.0 g dose, equivalent to 6.85 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions caused by inhibition of P glycoprotein-mediated clearance or CYP-mediated clearance of medicinal products are unlikely (see section 5.2).

Decreases in valproic acid levels that may fall below the therapeutic range have been reported when valproic acid was co administered with carbapenem agents. The lowered valproic acid levels can lead to inadequate seizure control; therefore, concomitant use of ertapenem and valproic acid/sodium valproate is not recommended and alternative antibacterial or anti-convulsant therapies should be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

Adequate and well-controlled studies have not been performed in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo-foetal development, parturition or post-natal development. However, ertapenem should not be used during pregnancy unless the potential benefit outweighs the possible risk to the foetus.

Breast-feeding

Ertapenem is excreted in human milk. Because of the potential for adverse reactions on the infant, mothers should not breast-feed their infants while receiving ertapenem.

Fertility

There are no adequate and well-controlled studies regarding the effect of ertapenem use on fertility in men and women. Preclinical studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

INVANZ may influence patients' ability to drive and use machines. Patients should be informed that dizziness and somnolence have been reported with INVANZ (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Adults

The total number of patients treated with ertapenem in clinical studies was over 2 200 of which over 2 150 received a 1 g dose of ertapenem. Adverse reactions (i.e. considered by the investigator to be possibly, probably, or definitely related to the medicinal product) were reported in approximately 20 % of patients treated with ertapenem. Treatment was discontinued due to adverse reactions in 1.3 % of patients. An additional 476 patients received ertapenem as a single 1 g dose prior to surgery in a clinical study for the prophylaxis of surgical site infections following colorectal surgery.

For patients who received only INVANZ, the most common adverse reactions reported during therapy plus follow-up for 14 days after treatment was stopped were: diarrhoea (4.8 %), infused vein complication (4.5 %) and nausea (2.8 %).

For patients who received only INVANZ, the most frequently reported laboratory abnormalities and their respective incidence rates during therapy plus follow-up for 14 days after treatment was stopped were: elevations in ALT (4.6 %), AST (4.6 %), alkaline phosphatase (3.8 %) and platelet count (3.0 %).

Paediatric population (3 months to 17 years of age):

The total number of patients treated with ertapenem in clinical studies was 384. The overall safety profile is comparable to that in adult patients. Adverse reactions (i.e. considered by the investigator to be possibly, probably, or definitely related to the medicinal product) were reported in approximately 20.8 % of patients treated with ertapenem. Treatment was discontinued due to adverse reactions in 0.5 % of patients.

For patients who received only INVANZ, the most common adverse reactions reported during therapy plus follow-up for 14 days after treatment was stopped were: diarrhoea (5.2 %) and infusion site pain (6.1 %).

For patients who received only INVANZ, the most frequently reported laboratory abnormalities and their respective incidence rates during therapy plus follow-up for 14 days after treatment was stopped were: decreases in neutrophil count (3.0 %), and elevations in ALT (2.9 %) and AST (2.8 %).

Tabulated list of adverse reactions

For patients who received only INVANZ, the following adverse reactions were reported during therapy plus follow-up for 14 days after treatment was stopped:

Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1 000 to < 1/100); Rare (≥ 1/10 000 to < 1/1 000); Very rare (< 1/10 000); Not known (cannot be estimated from the available data).

	Adults 18 years of age and older	***Children and adolescents (3 months to 17 years of age)***
Infections and infestations	*Uncommon*: Oral candidiasis, candidiasis, fungal infection, pseudomembranous enterocolitis, vaginitis *Rare*: Pneumonia,	

	Adults 18 years of age and older	***Children and adolescents (3 months to 17 years of age)***
	dermatomycosis, postoperative wound infection, urinary tract infection	
Blood and lymphatic system disorders	*Rare*: Neutropenia, thrombocytopenia	
Immune system disorders	*Rare*: Allergy *Not known:* Anaphylaxis including anaphylactoid reactions	
Metabolism and nutrition disorders	*Uncommon*: Anorexia *Rare*: Hypoglycaemia	
Psychiatric disorders	*Uncommon*: Insomnia, confusion *Rare*: Agitation, anxiety, depression *Not known:* Altered mental status (including aggression, delirium, disorientation, mental status changes)	*Not known:* Altered mental status (including aggression)
Nervous system disorders	*Common*: Headache *Uncommon*: Dizziness, somnolence, taste perversion, seizure (see section 4.4) *Rare*: Tremor, syncope *Not known:* Hallucinations, depressed level of consciousness, dyskinesia, myoclonus, gait disturbance, encephalopathy (see section 4.4)	*Uncommon*: Headache *Not known:* Hallucinations
Eye disorders	*Rare:* Scleral disorder	
Cardiac disorders	*Uncommon*: Sinus bradycardia *Rare*: Arrhythmia, tachycardia	
Vascular disorders	*Common*: Infused vein complication, phlebitis/thrombophlebitis *Uncommon*: Hypotension *Rare*: Haemorrhage, increased blood pressure	*Uncommon*: Hot flush, hypertension
Respiratory, thoracic and mediastinal disorders	*Uncommon*: Dyspnoea, pharyngeal discomfort *Rare*: Nasal congestion, cough, epistaxis, rales/rhonchi, wheezing	
Gastrointestinal disorders	*Common*: Diarrhoea, nausea, vomiting *Uncommon*: Constipation, acid regurgitation, dry mouth, dyspepsia, abdominal pain *Rare*: Dysphagia, faecal incontinence, pelvic peritonitis *Not known:* Teeth staining	*Common*: Diarrhoea *Uncommon*: Faeces discoloured, melaena

	Adults 18 years of age and older	***Children and adolescents (3 months to 17 years of age)***
Hepatobiliary disorders	*Rare*: Cholecystitis, jaundice, liver disorder	
Skin and subcutaneous tissue disorders	*Common*: Rash, pruritus *Uncommon*: Erythema, urticaria *Rare*: Dermatitis, desquamation, hypersensitivity vasculitis *Not known:* Acute Generalised Exanthematous Pustulosis (AGEP), Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome)	*Common*: Diaper dermatitis *Uncommon*: Erythema, rash, petechiae
Musculoskeletal and connective tissue disorders	*Rare*: Muscle cramp, shoulder pain *Not known*: Muscular weakness	
Renal and urinary disorders	*Rare*: Renal insufficiency, acute renal insufficiency	
Pregnancy, puerperium and perinatal conditions	*Rare:* Abortion	
Reproductive system and breast disorders	*Rare*: Genital bleeding	
General disorders and administration site conditions	*Uncommon*: Extravasation, asthenia/fatigue, fever, oedema/swelling, chest pain *Rare*: Injection-site induration, malaise	*Common*: Infusion site pain *Uncommon*: Infusion site burning, infusion site pruritus, infusion site erythema, injection site erythema, infusion site warmth
Investigations		
Chemistry	*Common*: Elevations in ALT, AST, alkaline phosphatase *Uncommon*: Increases in total serum bilirubin, direct serum bilirubin, indirect serum bilirubin, serum creatinine, serum urea, serum glucose *Rare*: Decreases in serum bicarbonate, serum creatinine and serum potassium; increases in serum LDH, serum phosphorus, serum potassium	*Common*: Elevations in ALT and AST
Haematology	*Common*: Elevation in platelet count *Uncommon*: Decreases in white blood cells, platelet count, segmented neutrophils, haemoglobin and haematocrit; increases in eosinophils, activated partial thromboplastin	*Common*: Decreases in neutrophil count *Uncommon*: Increases in platelet count, activated partial thromboplastin time, prothrombin time, decreases in haemoglobin

	Adults 18 years of age and older	***Children and adolescents (3 months to 17 years of age)***
	time, prothrombin time, segmented neutrophils and white blood cells *Rare*: Decrease in lymphocytes; increases in band neutrophils, lymphocytes, metamyelocytes, monocytes, myelocytes; atypical lymphocytes	
Urinalysis	*Uncommon*: Increases in urine bacteria, urine white blood cells, urine epithelial cells and urine red blood cells; urine yeast present *Rare*: Increase in urobilinogen	
Miscellaneous	*Uncommon*: Positive *Clostridioides difficile* toxin	

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No specific information is available on the treatment of overdose with ertapenem. Overdosing of ertapenem is unlikely. Intravenous administration of ertapenem 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 reactions. In paediatric clinical studies, a single intravenous (IV) dose of 40 mg/kg up to a maximum of 2 g did not result in toxicity.

However, in the event of an overdose, treatment with INVANZ should be discontinued and general supportive treatment given until renal elimination takes place.

Ertapenem can be removed to some extent by haemodialysis (see section 5.2); however, no information is available on the use of haemodialysis to treat overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

General properties

Pharmacotherapeutic group: Antibacterials for systemic use, carbapenems, ATC code: J01DH03

Mechanism of action
Ertapenem inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). In *Escherichia coli*, affinity is strongest to PBPs 2 and 3.

Pharmacokinetic/Pharmacodynamic (PK/PD) relationship
Similar to other beta-lactam antimicrobial agents, the time that the plasma concentration of ertapenem exceeds the MIC of the infecting organism has been shown to best correlate with efficacy in pre-clinical PK/PD studies.

Mechanism of resistance
For species considered susceptible to ertapenem, resistance was uncommon in surveillance studies in Europe. In resistant isolates, resistance to other antibacterial agents of the carbapenem class was seen in some but not all isolates. Ertapenem is effectively stable to hydrolysis by most classes of beta-lactamases, including penicillinases, cephalosporinases and extended spectrum beta-lactamases, but not metallo-beta-lactamases.

Methicillin-resistant staphylococci and enterococci are resistant to ertapenem, owing to PBP target insensitivity; *P. aeruginosa* and other non-fermentative bacteria are generally resistant, probably owing to limited penetration and to active efflux.

Resistance is uncommon in Enterobacteriaceae and ertapenem is generally active against those with extended-spectrum beta-lactamases (ESBLs). Resistance can however be observed when ESBLs or other potent beta-lactamases (e.g., AmpC types) are present in conjunction with reduced permeability, arising by the loss of one or more outer membrane porins, or with up-regulated efflux. Resistance can also arise via the acquisition of beta-lactamases with significant carbapenem-hydrolysing activity (e.g., IMP and VIM metallo-beta-lactamases or KPC types), though these are rare.

The mechanism of action of ertapenem differs from that of other classes of antibiotics, such as quinolones, aminoglycosides, macrolides and tetracyclines. There is no target-based cross-resistance between ertapenem and these substances. However, micro-organisms may exhibit resistance to more than one class of antibacterial agents when the mechanism is, or includes, impermeability to some compounds and/or an efflux pump.

Breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for ertapenem and are listed here: https://www.eucast.org/clinical_breakpoints.

The prescribers are informed that local MIC breakpoints, if available, should be consulted.

Microbiological susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. Localised clusters of infections due to carbapenem-resistant organisms have been

reported in the European Union. The information below gives only approximate guidance on the probability as to whether the micro-organism will be susceptible to ertapenem or not.

Commonly susceptible species:
Gram-positive aerobes: Methicillin-susceptible-staphylococci (including *Staphylococcus aureus)** *Streptococcus agalactiae** *Streptococcus pneumoniae**† *Streptococcus pyogenes*
Gram-negative aerobes: *Citrobacter freundii* *Enterobacter aerogenes* *Enterobacter cloacae* *Escherichia coli** *Haemophilus influenzae** *Haemophilus parainfluenzae* *Klebsiella oxytoca* *Klebsiella pneumoniae** *Moraxella catarrhalis** *Morganella morganii* *Proteus mirabilis** *Proteus vulgaris* *Serratia marcescens*
Anaerobes: *Clostridium* species (excluding *C. difficile*)* *Eubacterium* species* *Fusobacterium* species* *Peptostreptococcus* species* *Porphyromonas asaccharolytica** *Prevotella* species*
Species for which acquired resistance may be a problem:
Gram-positive aerobes: Methicillin-resistant staphylococci +#
Anaerobes: *Bacteroides fragilis* and species in the *B. fragilis* Group*
Inherently resistant organisms:
Gram-positive aerobes: *Corynebacterium jeikeium* Enterococci including *Enterococcus faecalis* and *Enterococcus faecium*
Gram-negative aerobes: *Aeromonas* species *Acinetobacter* species *Burkholderia cepacia* *Pseudomonas aeruginosa* *Stenotrophomonas maltophilia*
Anaerobes: *Lactobacillus* species
Others: *Chlamydia* species *Mycoplasma* species *Rickettsia* species *Legionella* species

*Activity has been satisfactorily demonstrated in clinical studies.

†The efficacy of INVANZ in the treatment of community acquired pneumonia due to penicillin-resistant *Streptococcus pneumoniae* has not been established.

+frequency of acquired resistance > 50 % in some Member States.

#Methicillin-resistant staphylococci (including MRSA) are always resistant to beta-lactams.

Information from clinical studies

Efficacy in Paediatric Studies
Ertapenem was evaluated primarily for paediatric safety and secondarily for efficacy in randomised comparative, multicentre studies in patients 3 months to 17 years of age.

The proportion of patients with a favourable clinical response assessment at post-treatment visit in the clinical MITT population is shown below:

Disease Stratum[†]	Age Stratum	Ertapenem		Ceftriaxone	
		n/m	%	n/m	%
Community Acquired Pneumonia (CAP)	3 to 23 months	31/35	88.6	13/13	100.0
	2 to 12 years	55/57	96.5	16/17	94.1
	13 to 17 years	3/3	100.0	3/3	100.0
Disease Stratum	Age Stratum	Ertapenem		Ticarcillin/clavulanate	
		n/m	%	n/m	%
Intra-abdominal Infections (IAI)	2 to 12 years	28/34	82.4	7/9	77.8
	13 to 17 years	15/16	93.8	4/6	66.7
Acute Pelvic Infections (API)	13 to 17 years	25/25	100.0	8/8	100.0

[†]This includes 9 patients in the ertapenem group (7 CAP and 2 IAI), 2 patients in the ceftriaxone group (2 CAP), and 1 patient with IAI in the ticarcillin/clavulanate group with secondary bacteraemia at entry into the study.

5.2 Pharmacokinetic properties

Plasma concentrations
Average plasma concentrations of ertapenem following a single 30 minute intravenous infusion of a 1 g dose in healthy young adults (25 to 45 years of age) were 155 micrograms/mL (C_{max}) at 0.5 hour post-dose (end of infusion), 9 micrograms/mL at 12 hour post-dose, and 1 microgram/mL at 24 hour post-dose.

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 intravenous doses ranging from 0.5 to 2 g daily.

Average plasma concentrations of ertapenem following a single 30 minute intravenous infusion of a 15 mg/kg (up to a maximum dose of 1 g) dose in patients 3 to 23 months of age were 103.8 micrograms/mL (C_{max}) at 0.5 hour post-dose (end of infusion), 13.5 micrograms/mL at 6 hour post-dose, and 2.5 micrograms/mL at 12 hour post-dose.

Average plasma concentrations of ertapenem following a single 30 minute intravenous infusion of a 15 mg/kg (up to a maximum dose of 1 g) dose in patients 2 to 12 years of age were 113.2 micrograms/mL (C_{max}) at 0.5 hour post-dose (end of

infusion), 12.8 micrograms/mL at 6 hour post-dose, and 3.0 micrograms/mL at 12 hour post-dose.

Average plasma concentrations of ertapenem following a single 30 minute intravenous infusion of a 20 mg/kg (up to a maximum dose of 1 g) dose in patients 13 to 17 years of age were 170.4 micrograms/mL (C_{max}) at 0.5 hour post-dose (end of infusion), 7.0 micrograms/mL at 12 hour post-dose, and 1.1 microgram/mL at 24 hour post-dose.

Average plasma concentrations of ertapenem following a single 30 minute intravenous infusion of a 1 g dose in three patients 13 to 17 years of age were 155.9 micrograms/mL (C_{max}) at 0.5 hour post-dose (end of infusion), and 6.2 micrograms/mL at 12 hour post-dose.

Distribution

Ertapenem is highly bound to human plasma proteins. In healthy young adults (25 to 45 years of age), the protein binding of ertapenem decreases, as plasma concentrations increase, from approximately 95 % bound at an approximate plasma concentration of < 50 micrograms/mL to approximately 92 % bound at an approximate plasma concentration of 155 micrograms/mL (average concentration achieved at the end of infusion following 1 g intravenously).

The volume of distribution (V_{dss}) of ertapenem in adults is approximately 8 litres (0.11 litre/kg) and 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.

Concentrations of ertapenem achieved in adult skin blister fluid at each sampling point on the third day of 1 g once daily intravenous doses showed a ratio of AUC in skin blister fluid: AUC in plasma of 0.61.

In vitro studies indicate that the effect of ertapenem on the plasma protein binding of highly protein bound medicinal products (warfarin, ethinyl estradiol, and norethindrone) was small. The change in binding was < 12 % at peak plasma ertapenem concentration following a 1 g dose. *In vivo*, probenecid (500 mg every 6 hours) decreased the bound fraction of ertapenem in plasma at the end of infusion in subjects administered a single 1 g intravenous dose from approximately 91 % to approximately 87 %. The effects of this change are anticipated to be transient. A clinically significant interaction due to ertapenem displacing another medicinal product or another medicinal product displacing ertapenem is unlikely.

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.

Biotransformation
In healthy young adults (23 to 49 years of age), after intravenous 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 dehydropeptidase-I-mediated 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 CYP isoforms: 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4.

Elimination
Following administration of a 1 g radiolabelled intravenous dose of ertapenem to healthy young adults (23 to 49 years of age), approximately 80 % is recovered in urine and 10 % in faeces. Of the 80 % recovered in urine, approximately 38 % is excreted as unchanged ertapenem and approximately 37 % as the ring-opened metabolite.

In healthy young adults (18 to 49 years of age) and patients 13 to 17 years of age given a 1 g intravenous dose, the mean plasma half-life is approximately 4 hours. The mean plasma half-life in children 3 months to 12 years of age is approximately 2.5 hours. Average concentrations of ertapenem in urine exceed 984 micrograms/mL during the period 0 to 2 hours post-dose and exceed 52 micrograms/mL during the period 12 to 24 hours post-administration.

Special populations

Gender
The plasma concentrations of ertapenem are comparable in men and women.

Elderly

Plasma concentrations following a 1 g and 2 g intravenous dose of ertapenem are slightly higher (approximately 39 % and 22 %, respectively) in healthy elderly adults (≥ 65 years) relative to young adults (< 65 years). In the absence of severe renal impairment, no dosage adjustment is necessary in elderly patients.

Paediatric population

Plasma concentrations of ertapenem are comparable in paediatric patients 13 to 17 years of age and adults following a 1 g once daily intravenous 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. 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 show 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 intravenous 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 intravenous dose in adults (see Plasma concentrations). 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 and plasma concentrations at the midpoint of the dosing interval in patients 3 months to 12 years of age were comparable to those in young healthy adults receiving a 1 g intravenous dose of ertapenem.

Hepatic impairment

The pharmacokinetics of ertapenem in patients with hepatic impairment 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 recommended in patients with hepatic impairment.

Renal impairment
Following a single 1 g intravenous dose of ertapenem in adults, AUCs of total ertapenem (bound and unbound) and of unbound ertapenem are similar in patients with mild renal impairment (Cl_{cr} 60 to 90 mL/min/1.73 m^2) compared with healthy subjects (ages 25 to 82 years). AUCs of total ertapenem and of unbound ertapenem are increased in patients with moderate renal impairment (Cl_{cr} 31 to 59 mL/min/1.73 m^2) approximately 1.5-fold and 1.8-fold, respectively, compared with healthy subjects. AUCs of total ertapenem and of unbound ertapenem are increased in patients with severe renal impairment (Cl_{cr} 5 to 30 mL/min/1.73 m^2) approximately 2.6-fold and 3.4-fold, respectively, compared with healthy subjects. AUCs of total ertapenem and of unbound ertapenem are increased in patients who require haemodialysis approximately 2.9-fold and 6.0-fold, respectively, between dialysis sessions, compared with healthy subjects. Following a single 1 g intravenous 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 impairment.

There are inadequate data on the safety and efficacy of ertapenem in patients with advanced renal impairment and patients who require haemodialysis to support a dose recommendation. Therefore, ertapenem should not be used in these patients.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development. Decreased neutrophil counts, however, occurred in rats that received high doses of ertapenem, which was not considered a significant safety issue.

Long term studies in animals to evaluate the carcinogenic potential of ertapenem have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium bicarbonate (E500)

Sodium hydroxide (E524) to adjust pH to 7.5

6.2 Incompatibilities

Do not use solvents or infusion fluids containing dextrose for reconstitution or administration of ertapenem.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years.

After reconstitution: Diluted solutions should be used immediately. If not used immediately, in use storage times are the responsibility of the user. Diluted solutions (approximately 20 mg/mL ertapenem) are physically and chemically stable for 6 hours at room temperature (25°C) or for 24 hours at 2 to 8 °C (in a refrigerator). Solutions should be used within 4 hours of their removal from the refrigerator. Do not freeze solutions of INVANZ.

6.4 Special precautions for storage

Do not store above 25 °C.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

15 mL Type I glass vials with a grey butyl stopper and a white plastic cap on a coloured aluminium band seal.

Supplied in packs of 1 vial or 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Instructions for use:

For single use only.

Reconstituted solutions should be diluted in sodium chloride 9 mg/mL (0.9 %) solution immediately after preparation.

Preparation for intravenous administration:

INVANZ must be reconstituted and then diluted prior to administration.

Adults and adolescents (13 to 17 years of age)

Reconstitution

Reconstitute the contents of a 1 g vial of INVANZ with 10 mL of water for injection or sodium chloride 9 mg/mL (0.9 %) solution to yield a reconstituted solution of approximately 100 mg/mL. Shake well to dissolve. (See section 6.4).

Dilution

For a 50 mL bag of diluent: For a 1 g dose, immediately transfer contents of the reconstituted vial to a 50 mL bag of sodium chloride 9 mg/mL (0.9 %) solution; or

For a 50 mL vial of diluent: For a 1 g dose, withdraw 10 mL from a 50 mL vial of sodium chloride 9 mg/mL (0.9 %) solution and discard. Transfer the contents of the reconstituted 1 g vial of INVANZ to the 50 mL vial of sodium chloride 9 mg/mL (0.9 %) solution.

Infusion

Infuse over a period of 30 minutes.

Children (3 months to 12 years of age)

Reconstitution

Reconstitute the contents of a 1 g vial of INVANZ with 10 mL of water for injection or sodium chloride 9 mg/mL (0.9 %) solution to yield a reconstituted solution of approximately 100 mg/mL. Shake well to dissolve. (See section 6.4).

Dilution

For a bag of diluent: Transfer a volume equal to 15 mg/kg of body weight (not to exceed 1 g/day) to a bag of sodium chloride 9 mg/mL (0.9 %) solution for a final concentration of 20 mg/mL or less; or

For a vial of diluent: Transfer a volume equal to 15 mg/kg of body weight (not to exceed 1 g/day) to a vial of sodium chloride 9 mg/mL (0.9 %) solution for a final concentration of 20 mg/mL or less.

Infusion

Infuse over a period of 30 minutes.

Compatibility of INVANZ with intravenous solutions containing heparin sodium and potassium chloride has been demonstrated.

The reconstituted solutions should be inspected visually for particulate matter and discolouration prior to administration, whenever the container permits. Solutions of INVANZ range from colourless to pale yellow. Variations of colour within this range do not affect potency.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme (UK) Limited
120 Moorgate
London
EC2M 6UR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 53095/0028

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

25/09/2025