SCHEDULING STATUS

S4

1 NAME OF THE MEDICINAL PRODUCT

INVANZ® Sterile Powder for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains ertapenem sodium equivalent to 1 g of ertapenem free acid.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for injection

Solid, white to off-white essentially uniform cake.

4 CLINICAL PARTICULARS

4.1 Therapeutic indication

INVANZ is indicated for the treatment of adult patients with the following moderate to severe infections caused by susceptible strains of the designated micro-organisms (see section 4.2):

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

Complicated Skin and Skin Structure Infections including diabetic lower extremity and diabetic foot infections due to *Staphylococcus aureus (*methicillin susceptible strains only*), Streptococcus agalactiae, Streptococcus pyogenes, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Porphyromonas asaccharolytica* or *Peptostreptococcus species.*

Community Acquired Pneumonia due to *Streptococcus pneumoniae* (penicillin susceptible strains only) including cases with concurrent bacteraemia, *Moraxella catarrhalis.* If Community Acquired Pneumonia is caused by *Haemophilus influenzae*, INVANZ should be used only following confirmation of culture and sensitivity results.

Complicated Urinary Tract Infections including pyelonephritis due to *Escherichia coli,* including cases with concurrent bacteraemia or *Klebsiella pneumoniae.*

Acute Pelvic Infections including Post-partum Endomyometritis, Septic Abortion and Post-surgical Gynaecologic Infections due to *Streptococcus agalactiae, Escherichia coli, Bacteroides fragilis, Porphyromonas asaccharolytica, Peptostreptococcus* species or *Prevotelia bivia.*

Paediatric use

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

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

- Acute Pelvic Infections.

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 (ertapenem) may be initiated empirically before results of these tests are known; once results become available, antimicrobial therapy should be adjusted accordingly.

4.2 Posology and method of administration

Posology

The 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 patient 3 months to 12 years of age is 15 mg/kg twice daily (not to exceed 1g/day).

The usual duration of therapy with INVANZ is 3 to14 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.

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.

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. INVANZ should be infused over a period of 30 minutes. For instructions on dilution of the product before administration, see section 6.6.

Dosage Guidelines for Adults and Paediatric Patients with Normal Renal Function and Body Weight**			
Infection	**Daily Dose (IV or IM) Adults and Paediatric Patients 13 years of age and older**	**Daily Dose (IV or IM) Paediatric Patients 3 months to 12 years of age**	**Recommended Duration of Total Antimicrobial Treatment**
Complicated Intra-abdominal Infections	1 g	15 mg/kg twice daily§	5 to 14 days
Complicated Skin and Skin Structure Infections including diabetic lower extremity and diabetic foot infections	1 g	15 mg/kg twice daily§	7 to 14 days‖

Community Acquired Pneumonia	1 g	15 mg/kg twice daily§	10 to 14 days†
Complicated Urinary Tract Infections including pyelonephritis	1 g	15 mg/kg twice daily§	10 to 14 days†
Acute Pelvic Infections including postpartum endomyometritis, septic abortion and post-surgical gynaecologic infections	1 g	15 mg/kg twice daily§	3 to 10 days

**defined as creatinine clearance > 90 mL/min/1,73 m^2.

†duration includes a possible switch to an appropriate oral therapy once clinical improvement has been demonstrated.

§not to exceed 1 g/day.

‖patients with diabetic foot infections received up to 28 days of treatment (parenteral or parenteral plus oral switch therapy).

Special populations

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.

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 hemofiltration. 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.

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

Females: (0,85) x (value calculated for males)

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

No dosage adjustment is recommended in patients with impaired hepatic function (see section 5.1 Pharmacokinetics, Hepatic insufficiency).

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

4.3 Contraindications

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

Due to the use of lidocaine (lignocaine) hydrochloride 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 hydrochloride.)

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

INVANZ is not recommended in the treatment of meningitis due to lack of sufficient CSF penetration.

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 INCLUDING INVANZ. 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 WITH EPINEPHRINE (ADRENALINE), OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION. OTHER THERAPY MAY ALSO BE ADMINISTERED AS INDICATED.**

Seizures and other CNS adverse experiences have been reported during treatment with INVANZ (see below and section 4.8). 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 days 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 disorder. 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.

Pseudomembranous colitis (antibiotic-associated colitis) has been reported with INVANZ 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 INVANZ.

Treatment with INVANZ alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to medicine discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, parenteral nutrition and treatment with an antibacterial medicine clinically effective against *Clostridium difficile* colitis.

Lidocaine (Lignocaine) hydrochloride is the diluent for intramuscular administration of INVANZ. Refer to the prescribing information for lidocaine (lignocaine) hydrochloride.

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.

Co-administration of carbapenems, including ertapenem, to patients receiving valproic acid or divalproex sodium results in a reduction in 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. The concomitant use of ertapenem and valproic acid/divalproex sodium is not recommended. Antibacterials other than carbapenems should be considered to treat infections in patients whose seizures are well controlled on valproic acid or divalproex sodium. If administration of INVANZ is necessary, supplemental anti-convulsant therapy should be considered (see section 4.5).

Caution should be taken when administering INVANZ intramuscularly, to avoid inadvertent injection into a blood vessel (see section 4.2).

4.5 Interaction with other medicines and other forms of interaction

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 Distribution and Metabolism).

No specific clinical drug interaction studies have been conducted.

Valproate

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.

INVANZ should not be co-administered with valproic acid or divalproex sodium. The valproic acid concentrations may drop below the therapeutic range as a result of this interaction, therefore increasing the risk of breakthrough seizures (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

Breastfeeding

Ertapenem is excreted in human milk (see section 5.2 Distribution). Safety in nursing mothers has not been established.

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 1 900 of which over 1 850 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 INVANZ. INVANZ was discontinued due to adverse experiences thought to be drug-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 drug-related adverse experiences were reported during parenteral therapy in adult patients treated with ertapenem: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (≤ 1/ 10 000), including isolated reports, not known (cannot be estimated from available data).

Common

Nervous system disorders: headache

Vascular disorders: infused vein complication, phlebitis/thrombophlebitis

Gastrointestinal disorders: diarrhoea, nausea, vomiting.

Uncommon

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 INVANZ.

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 post-treatment follow-up period, drug-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).

Paediatric patients

The total number of paediatric patients treated with INVANZ 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 INVANZ:

Common

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, drug-related adverse experiences in patients treated with INVANZ were no different than those listed above.

Post-marketing adverse events

The following post-marketing adverse experiences have been reported:

Immune system disorders: 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)

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, connective tissue and bone 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 post-treatment 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 (conjugated), total serum bilirubin, eosinophils, indirect serum bilirubin (unconjugated), PTT, urine bacteria, serum urea, serum creatinine, serum glucose, monocytes, urine epithelial cells, urine red blood cells; decreases in segmented neutrophils, white blood cells, haematocrit, haemoglobin and platelet count.

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 laboratories 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 increase in eosinophils.

4.9 Overdose

No specific information is available on the treatment of overdosage with INVANZ.

In the event of overdose, INVANZ should be discontinued, and general supportive care 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.20.1.1 Broad and medium spectrum antibiotics

Ertapenem is a synthetic, long-acting, 1-β methyl-carbapenem that is structurally related to beta-lactam antibiotics, such as penicillins and cephalosporins. 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.

Microbiology

Ertapenem has *in vitro* activity against a wide range of gram-positive and gram-negative aerobic and anaerobic bacteria. 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.

Resistant Organisms

Corynebacterium spp, *Enterococcus* spp (including *Enterococcus faecalis* and *Enterococcus faecium*), methicillin resistant S*taphylococcus aureus*, methicillin resistant coagulase negative S*taphylococcus*, *Acinetobacter* spp, *Pseudomonas* spp, S*tenotrophomonas maltophilia.*

5.2 Pharmacokinetic properties

Absorption

Ertapenem, reconstituted with 1 % lidocaine hydrochloride injection, USP (in saline without epinephrine), is well absorbed. Following IM administration of ertapenem at the recommended dose of 1 g, the mean bioavailability is approximately 92 % and the mean peak plasma concentrations (C_{max}) are reached in approximately 2 hours (T_{max}).

Distribution

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

Average plasma concentrations (µg/mL) of ertapenem following a single 30-minute IV infusion of a 1 or 2 g dose and IM administration of a single 1 g dose in healthy young adults are presented in **Table 1**.

TABLE 1

Plasma Concentrations of Ertapenem in Adults 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
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 (µg/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 (µg/mL)								
	0,5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	18 hr	24 hr
3 to 23 months									
(15 mg/kg)†	103,8	57,3	43,6	23,7	13,5	8,2	2,5	-	103,8
(20 mg/kg†	126,8	87,6	58,7	28,4	-	12,0	3,4	0,4	126,8
(40 mg/kg)‡	199,1	144,1	95,7	58,0	-	20,2	7,7	0,6	199,1

2 to 12 years									
(15 mg/kg)†	113,2	63,9	42,1	21,9	12,8	7,6	3,0	-	113,2
(20 mg/kg)†	147,6	97,6	63,2	34,5	-	12,3	4,9	0,5	147,6
(40 mg/kg)‡	241,7	152,7	96,3	55,6	-	18,8	7,2	0,6	241,7
13 to 17 years									
(20 mg/kg)†	170,4	98,3	67,8	40,4	-	16,0	7,0	1,1	170,4
(1 g)§	155,9	110,9	74,8	-	24,0	-	6,2	-	155,9
(40 mg/kg)‡	255,0	188,7	127,9	76,2	-	31,0	15,3	2,1	255,0

*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 apparent 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.

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 result in a ratio of AUC in skin blister fluid to AUC in plasma of 0,61.

Ertapenem penetrates into breast milk.

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).

Metabolism

In healthy young adults, after IV infusion of radio-labelled 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.

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).

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 radio-labelled 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 post-dose and exceed 52 µg/mL during the period 12 to 24 hours post-dose.

Special populations

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 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 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 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 to 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 to 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 to 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 patients with advanced or end-stage renal insufficiency (see section 4.2).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

sodium bicarbonate

sodium hydroxide

6.2 Incompatibilities

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

24 months

6.4 Special precautions for storage

Before reconstitution

Store lyophilised powder at or below 25 °C.

Reconstituted and infusion solutions

The reconstituted solution, immediately diluted in 0,9 % Sodium Chloride Injection (see section 4.2), may be stored at room temperature (25 °C), and used within 6 hours or stored for 24 hours under refrigeration (5 °C) and used within 4 hours after removal from refrigeration. Solutions of INVANZ should not be frozen. Any unused portion of solutions of INVANZ should be discarded.

Keep out of reach of children.

6.5 Nature and contents of container

INVANZ is supplied in 15 mL glass vials in pack size of 1's.

INVANZ Sterile Powder for Injection: solid, white to off-white essentially uniform cake.

INVANZ reconstituted solution: the reconstituted solution ranges from colourless to pale yellow and is essentially free of visual foreign matter particles.

6.6 Special precautions for disposal and 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 (154 mmol/L) 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 (154 mmol/L).
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 maximum 3,2 mL of 2 % lidocaine hydrochloride injection*** (**without epinephrine**). Shake vial

thoroughly to form solution. This represents the maximum recommended dose of lidocaine.

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**.

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

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 (154 mmol/L) 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 (154 mmol/L) 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 maximum 3,2 mL of 2,0 % lidocaine hydrochloride injection*** (**without epinephrine**). Shake vial thoroughly to form solution. This represents the maximum recommended dose of lidocaine.
2. Immediately withdraw a volume equal to 15 mg/kg of body weight (not to exceed 1 g/day) and administer by deep intramuscular injection into a large muscle mass (such as the gluteal muscles or lateral part of the thigh).
3. The reconstituted IM solution should be used within 1 hour after preparation. **Note: The reconstituted solution should not be administered intravenously.**

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

Parenteral drug products should be inspected visually for particulate matter and discoloration 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 HOLDER OF CERTIFICATE OF REGISTRATION

MSD (Pty) Ltd

117 16th Road

Halfway House

1685

South Africa

8 REGISTRATION NUMBER

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9 DATE OF FIRST AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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