PROFESSIONAL INFORMATION

INVABEX

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

INVABEX 1 g sterile powder for solution for injection or infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains ertapenem sodium equivalent to ertapenem 1 g.

Excipient with known effect:

Each 1 g dose contains approximately 6,0 millimoles of sodium (approximately 137 mg).

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

White to yellowish powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adult patients

INVABEX is indicated for the treatment of adult patients with the following moderate to severe infections, caused by susceptible strains of the designated microorganisms (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 pneumonia* (penicillin susceptible strains only) including cases with concurrent bacteraemia, *Moraxella catarrhalis.* If community acquired pneumonia is caused by *Haemophilus influenzae*, INVABEX should be used only after 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 postpartum endomyometritis, septic abortion and post-surgical gynaecologic infections due to *Streptococcus agalactiae, Escherichia coli, Bacteroides fragilis, Porphyromonas asaccharolytica, Peptostreptococcus* species or *Prevotella bivia.*

Paediatric patients

INVABEX is indicated in paediatric patients 3 months to 17 years of age with the following infections (see "*Adult patients***"** above for susceptible organisms):

- 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 INVABEX 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 usual dose of INVABEX in patients 13 years of age and older is 1 gram (g) given once a day.

The usual dose of INVABEX in patients 3 months - 12 years of age is 15 mg/kg twice daily (not to exceed 1 g/day).

Intramuscular (IM) administration of INVABEX may be used as an alternative to intravenous (IV) administration in the treatment of those infections for which intramuscular therapy is appropriate.

Dosage guidelines for adults and paediatric patients with normal renal function* and body mass			
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 - 12 years of age**	**Recommended duration of total antimicrobial treatment**
Complicated intra-abdominal infection	1 g	15 mg/kg twice daily§	5 - 14 days‖
Complicated skin and skin structure infections including diabetic lower extremity and diabetic foot infections	1 g	15 mg/kg twice daily§	7 - 14 days‖
Community acquired pneumonia	1 g	15 mg/kg twice daily§	10 - 14 days‖

Complicated urinary tract infections including pyelonephritis	1 g	15 mg/kg twice daily[§]	10 - 14 days[‖]
Acute pelvic infections including postpartum endomyometritis septic abortion and post-surgical gynaecologic infections	1 g	15 mg/kg twice daily[§]	3 - 10 days[‖]

[*] Defined as creatinine clearance greater than 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

Patients with renal insufficiency

INVABEX may be used for the treatment of infections in adult patients with renal insufficiency.

In adult patients whose creatinine clearance is greater than 30 mL/min/1,73 m^2, no dosage adjustment is necessary.

Adult patients with advanced renal insufficiency (creatinine clearance less than or equal to 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

Following a single 1 g IV dose of ertapenem given immediately prior to a haemodialysis session, approximately 30 % of the dose may be recovered in the dialysate.

When adult patients on haemodialysis are given the recommended daily dose of 500 mg of INVABEX within 6 hours prior to haemodialysis, a supplementary dose of 150 mg is recommended after the haemodialysis session. If INVABEX is given at least 6 hours before haemodialysis, no supplementary dose is needed.

No data are available in patients undergoing peritoneal dialysis or haemofiltration.

There are also no data in paediatric patients on haemodialysis.

When only the serum creatinine is available, the following formula** may be used to calculate 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)

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

Patients with hepatic impairment

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

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

Elderly

The recommended dose of INVABEX should be administered, except in cases of severe renal impairment (see Patients with renal impairment above).

Paediatric population

There is little experience with ertapenem (as in INVABEX) in children less than two years of age; thus, particular care should be taken to establish the susceptibility of the infecting organism(s) to ertapenem. INVABEX should not be used in infants under the age of 3 months, as no data are available (see section 4.3 and 4.4).

Method of administration

For instructions on the preparation of INVABEX before administration, see section 6.6.
INVABEX may be administered by intravenous (IV) infusion or intramuscular (IM) injection.
When administered intravenously, INVABEX should be infused over a period of 30 minutes.
The usual duration of therapy with INVABEX is 3 to 14 days, but it may vary according to the type of infection and causative pathogen(s). When clinically indicated, a switch to an appropriate oral antimicrobial medicine may be implemented if clinical improvement has been observed.

4.3 Contraindications

INVABEX is contraindicated in:

- hypersensitivity to ertapenem or to any of the excipients of INVABEX. (see section 6.1)
- hypersensitivity to beta-lactam antibiotics
- patients with known bacterial meningitis, due to lack of sufficient cerebrospinal fluid (CSF) penetration
- INVABEX is not recommended in infants under 3 months of age, as no data are available.

Due to the use of lidocaine (lignocaine) hydrochloride as a diluent, INVABEX administered intramuscularly is contraindicated in patients with a known hypersensitivity to amide type local

anaesthetics and in patients with severe shock or heart block. (Refer to the professional information for lidocaine (lignocaine) hydrochloride).

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-LACTAM ANTIBIOTICS, INCLUDING INVABEX.

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 INVABEX, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER BETA-LACTAMS AND OTHER ALLERGENS. IF AN ALLERGIC REACTION TO INVABEX OCCURS, DISCONTINUE INVABEX IMMEDIATELY.

SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH ADRENALINE (EPINEPHRINE), OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION. OTHER THERAPY MAY ALSO BE ADMINISTERED AS INDICATED.

Prescribers must adhere to the principles of antibiotic stewardship.

Hypersensitivity reactions can also progress to Kounis syndrome, (acute coronary syndrome accompanying allergic reaction) and linear IgA associated with the use of beta-lactam antibiotics, including INVABEX.

Superinfection

Prolonged use of INVABEX 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. See *Antibiotic-associated colitis* below.

Antibiotic-associated colitis

Pseudomembranous colitis (antibiotic-associated colitis) has been reported with ertapenem (contained in INVABEX) 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 INVABEX.

Treatment with INVABEX alters the normal flora of the colon and may permit overgrowth of clostridia. It has been demonstrated 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 discontinuation of INVABEX. 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.

Medicines that inhibit peristalsis should not be given.

Seizures

Seizures and other central nervous system (CNS) adverse experiences have been reported during treatment with ertapenem (as in INVABEX); see section 4.8. Seizures occur more frequently in elderly patients and those with pre-existing 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 INVABEX re-examined to determine whether it should be decreased or discontinued.

Encephalopathy

Encephalopathy has been reported with the use of INVABEX (see section 4.8). If ertapenem-induced encephalopathy is suspected (e.g. myoclonus, seizures, altered mental status, depressed level of consciousness), discontinuation of INVABEX 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 INVABEX and 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 enough to overcome this interaction. The concomitant use of INVABEX and valproic acid or divalproex sodium is not recommended (see section 4.5). 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 INVABEX is necessary, supplemental anticonvulsant therapy should be considered (see section 4.5).

Sub-optimal exposure

In 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 INVABEX for severe infections is limited.

Efficacy has not been established for the use of INVABEX in the treatment of community acquired pneumonia due to penicillin-resistant *Streptococcus pneumoniae,* or for diabetic foot infections with

concurrent osteomyelitis.

Caution should be taken with IM administration of INVABEX not to inject it inadvertently into a blood vessel (see section 4.2).

Lidocaine (lignocaine) hydrochloride is the diluent for intramuscular administration of INVABEX. Refer to the professional information for lidocaine hydrochloride.

Information on the inactive ingredients

INVABEX contains approximately 137 mg (approximately 6,0 millimoles) of sodium per vial, equivalent to 6,85 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Paediatric population

There is little experience with ertapenem (as in INVABEX) 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, INVABEX is therefore contraindicated in this age group (see section 4.3).

4.5 Interaction with other medicines and other forms of interaction

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). Ertapenem does not inhibit P-glycoprotein-mediated transport of digoxin or vinblastine and is not a substrate for P-glycoprotein-mediated transport.

No specific clinical drug interaction studies have been conducted.

Valproic acid

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

Probenecid

Probenecid inhibits the renal excretion of ertapenem, thereby increasing its plasma concentrations and prolonging its elimination half-life.

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). Safety in nursing mothers has not been established.

Fertility

There are no adequate and well controlled studies regarding the effect of ertapenem on fertility in men and women.

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.

Dizziness and somnolence are possible undesirable effects of INVABEX (see section 4.8). If affected, patients should be warned not to drive or operate machinery.

4.8 Undesirable effects

a. Summary of the safety profile

Adults

Most adverse experiences reported in 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 frequent 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 %).

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

The overall safety profile is comparable to that in adult patients. In clinical trials, most frequent medicine-related clinical adverse experiences reported during parenteral therapy were diarrhoea (5,5 %), infusion site pain (5,5 %) and infusion site erythema (2,6 %).

b. Tabulated list of adverse effects

ADULTS - 18 years of age and older

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	Less frequent	Oral candidiasis, candidiasis, fungal infection, pseudomembranous enterocolitis, vaginitis, pneumonia, dermatomycosis, postoperative wound infection, urinary tract infection, *C. difficile*-associated diarrhoea
Blood and lymphatic system disorders	Less frequent	Neutropaenia, thrombocytopaenia
Immune system disorders	Less frequent Frequency unknown	Allergy Anaphylaxis* including anaphylactoid reactions*

Metabolism and nutrition disorders	Less frequent	Anorexia, hypoglycaemia
Psychiatric disorders	Less frequent Frequency unknown	Insomnia, somnolence, confusion, agitation, anxiety, depression. Altered mental status* (including aggression, delirium, disorientation, mental status changes)*, hallucinations*
Nervous system disorders	Frequent Less frequent Frequency unknown	Headache Dizziness, taste perversion, seizure (see section 4.4), tremor, syncope Depressed level of consciousness*, dyskinesia*, myoclonus*, gait disturbance*, encephalopathy
Eye disorders	Less frequent	Scleral disorder
Cardiac disorders	Less frequent Frequency unknown	Sinus bradycardia, dysrhythmia, tachycardia Kounis syndrome
Vascular disorders	Frequent Less frequent	Infused vein complication, phlebitis/thrombophlebitis Hypotension, extravasation, haemorrhage, increased blood pressure
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea, pharyngeal discomfort, nasal congestion, cough, epistaxis, rales/rhonchi, wheezing
Gastrointestinal disorders	Frequent Less frequent Frequency unknown	Diarrhoea, nausea, vomiting Constipation, acid regurgitation, dry mouth, dyspepsia, abdominal pain, dysphagia, faecal incontinence, pelvic peritonitis Stained teeth*

Hepatobiliary disorders	Less frequent	Cholecystitis, jaundice, liver disorder
Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency unknown	Rash Erythema, urticaria, dermatitis, desquamation, pruritus, Linear IgA bullous dermatosis (LABD) Drug rash with eosinophilia and systemic symptoms (DRESS syndrome)*, toxic epidermal necrolysis*, Stevens-Johnson syndrome*, acute generalised exanthematous pustulosis (AGEP)*, hypersensitivity vasculitis*
Musculoskeletal, connective tissue and bone disorders	Frequent Frequency unknown	Muscle cramp, shoulder pain Muscular weakness*
Renal and urinary disorders	Less frequent	Renal insufficiency, acute renal insufficiency
Pregnancy, puerperium and perinatal conditions	Less frequent	Abortion
Reproductive system and breast disorders	Less frequent	Genital bleeding, vaginal pruritus
General disorders and administrative site conditions	Less frequent	Extravasation, asthenia/fatigue, fever, pain, oedema/swelling, chest pain, injection site induration, malaise

Investigations		
Chemistry:	Frequent	Elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase
	Less frequent	Increases in total serum bilirubin, direct serum bilirubin, indirect serum bilirubin, serum creatinine, serum urea, serum glucose, decreases in serum bicarbonate, serum creatinine and serum potassium; increases in serum Lactase dehydrogenase (LDH), serum phosphorus, serum potassium
Haematology	Frequent	Elevation in platelet count
	Less frequent	Decreases in white blood cells, platelet count, segmented neutrophils, haemoglobin and haematocrit; increases in eosinophils, activated partial thromboplastin time, prothrombin time (international normalised ration (INR)), segmented neutrophils and white blood cells, decrease in lymphocytes; increases in band neutrophils, lymphocytes, metamyelocytes, monocytes, myelocytes; atypical lymphocytes
Urinalysis	Less frequent	Increases in urine bacteria, urine white blood cells, urine epithelial cells and urine red blood cells; urine yeast present, increase in urobilinogen

Paediatric population

CHILDREN AND ADOLESCENTS (3 months - 17 years of age)

System Organ Class	Frequency	Side effects
Psychiatric disorders	Frequency unknown	Altered mental status (including aggression, hallucinations)

Nervous system disorders	Less frequent	Headache
Vascular disorders	Less frequent	Hot flush, hypertension
Gastrointestinal disorders	Frequent Less frequent	Diarrhoea, vomiting Faeces discoloured, melaena
Skin and subcutaneous tissue disorders	Frequent Less frequent	Diaper dermatitis, rash Erythema, rash, petechiae
General disorders and administrative site conditions	Frequent Less frequent	Infusion site pain, infusion site pruritus, infusion site erythema, infusion site swelling Infusion site burning, injection site erythema, infusion site warmth
Investigations **Chemistry:** **Haematology**	 Frequent Frequent Less frequent	 Elevations in ALT and AST Decreases in neutrophil count Increases in platelet count, activated partial thromboplastin time, prothrombin time (INR), decreases in haemoglobin, increase 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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

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

Management of overdose:

In the event of an overdose, INVABEX should be discontinued and general supportive treatment given until renal elimination takes place. INVABEX 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

Pharmacotherapeutic group: Antibacterials for systemic use, carbapenems

ATC code: J01DH03

Pharmacological classification: A 20.1.1 Broad and medium spectrum antibiotics

Mechanism of action

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

Ertapenem exerts bactericidal activity by inhibiting cell wall synthesis. This activity is mediated through the binding of ertapenem 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 *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 *Staphylococcus aureus*, methicillin resistant coagulase negative *Staphylococcus*, *Acinetobacter* spp, *Pseudomonas* spp, *Stenotrophomonas maltophilia.*

5.2 Pharmacokinetic properties

Absorption:

Ertapenem, reconstituted with 1 % lidocaine (lignocaine) hydrochloride injection, (in saline without adrenaline (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 less than 100 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 h	1 h	2 h	4 h	6 h	8 h	12 h	18 h	24 h
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									

The area under the plasma concentration curve (AUC) of ertapenem in adults increases nearly dose-proportionally over the 0,5 - 2 g dose range.

Ertapenem does not accumulate in adults after multiple IV doses ranging from 0,5 - 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 h	1 h	2 h	4 h	6 h	8 h	12 h	18 h	24 h
3 - 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)† (40 mg/kg)‡	147,6	97,6	63,2	34,5	-	12,3	4,9	0,5	147,6
	241,7	152,7	96,3	55,6	-	18,8	7,2	0,6	241,7
13 - 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 (Vdss) of ertapenem in adults is approximately 8 litres (0,11 litre/kg) and approximately 0,2 litre/kg in paediatric patients 3 months - 12 years of age and approximately 0,16 litre/kg in paediatric patients 13 - 17 years of age.

Ertapenem penetrates 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 resulted in a ratio of AUC in skin blister fluid to AUC in plasma of 0,61.

Ertapenem penetrates into breastmilk.

Ertapenem does not inhibit P-glycoprotein-mediated transport of digoxin or vinblastine and ertapenem is not a substrate for P-glycoprotein-mediated transport (see section 4.5).

Biotransformation:

After IV infusion of 1 g of radio labelled 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, 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 - 17 years of age is approximately 4 hours and approximately 2,5 hours in paediatric patients 3 months - 12 years of age.

Following IV administration of a 1 g 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 substance 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 - 2 hours post-dose and exceed 52 µg/mL during the period 12 - 24 hours post-dose.

Pharmacokinetics in special patient groups

Elderly

Plasma concentrations are slightly higher in elderly adults (65 years or older) relative to young adults (younger than 65 years). No dose adjustment is required for elderly patients.

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 (CrCl 60 - 90 mL/min/1,73 m^2) compared with healthy persons (ages 25 - 82 years).
The AUC is increased in patients with:

- moderate renal insufficiency (CrCl 31 - 59 mL/min/1,73 m^2), approximately 1,5 - fold compared with healthy persons
- advanced renal insufficiency (CrCl 5 - 30 mL/min/1,73 m^2), approximately 2,6 - fold compared with healthy persons
- end-stage renal insufficiency (CrCl less than 10 mL/min/1,73 m^2), approximately 2,9 - fold compared with healthy persons.

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).

Paediatric population

Plasma concentrations of ertapenem are comparable in paediatric patients 13 - 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 - 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 shows that a 1 g once daily dose of ertapenem achieves a pharmacokinetic profile in patients 13 - 17 years of age comparable to that of adults. The ratios (13 - 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 - 12 years of age are comparable to plasma concentrations at the midpoint of the dosing interval following a 1 g once daily IV dose in adults (see Distribution). The plasma clearance (mL/min/kg) of ertapenem in patients 3 months - 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 - 12 years of age was comparable to the AUC value in young healthy adults receiving a 1 g IV dose of ertapenem.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydrogen carbonate

Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

DO NOT USE SOLVENTS OR INFUSION FLUIDS CONTAINING DEXTROSE TO RECONSTITUTE OR FOR THE ADMINISTRATION OF ERTAPENEM.

In the absence of compatibility studies, this medicine should not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Before reconstitution

Shelf-life: 24 months.

Reconstituted solutions

From a microbial point of view, the product should be used immediately.

Reconstituted intramuscular injection solution:

The reconstituted IM solution should be used within 1 hour after preparation.

Reconstituted intravenous infusion solution:

If not used immediately, the storage time and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 - 8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

Diluted solutions (approximately 20 mg/mL ertapenem) are physically and chemically stable for 6 hours at or below 25 °C and for 24 hours at 2 - 8 °C (in a refrigerator). Solutions should be used within 4 hours of their removal from the refrigerator.

Do not freeze solutions of INVABEX.

For single use only.

6.4 Special precautions for storage

Powder:

Store at or below 25 ºC. Do not freeze.

Reconstituted and diluted solution:

See section 6.3.

6.5 Nature and contents of container

INVABEX is supplied in 20 mL colourless clear Type I glass vials with chlorobutyl rubber stoppers and aluminium/lacquered flip-off overseals.

Supplied in packs of 1 or 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for use

For single use only.

Do not mix or co-infuse INVABEX with other medicines.

Do not use diluents containing dextrose (α-d-glucose).

- **Adults and adolescents (13 - 17 years of age)**

Preparation for intravenous administration:

1. Reconstitute the contents of a 1 g vial of INVABEX with 10 mL of water for injection, 0,9 % sodium chloride injection (154 mmol/L) or bacteriostatic water for injection to yield a reconstituted solution of approximately 100 mg/mL. Shake well to dissolve (see section 6.3).
2. Immediately transfer contents of the reconstituted vial to 50 mL of 0,9 % sodium chloride injection (154 mmol/L).
3. Diluted solutions should be used immediately (see section 6.3).

4. Complete the infusion within 6 hours of reconstitution.

Administer the infusion for a period of 30 minutes.

The reconstituted solutions should be inspected visually for particulate matter and discolouration prior to administration, whenever the container permits. Solutions of INVABEX 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.

Preparation for intramuscular administration:

INVABEX must be reconstituted prior to administration.

1. Reconstitute the contents of a 1 g vial of INVABEX with 3,2 mL of 1,0 % or maximum 3,2 mL of 2 % lidocaine (lignocaine) hydrochloride injection*** (without adrenaline (epinephrine)). Shake vial thoroughly to form solution. This represents the maximum recommended dose of lidocaine (lignocaine).

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 professional information for lidocaine (lignocaine) hydrochloride.

- **Paediatric patients (3 months - 12 years of age)**

Preparation for intravenous administration:

INVABEX must be reconstituted and then diluted prior to administration.

Do not mix or co-infuse INVABEX with other medicines.

Do not use diluents containing dextrose (α-d-glucose).

1. Reconstitute the contents of a 1 g vial of INVABEX with 10 mL of water for injection, 0,9 % sodium chloride injection (154 mmol/L) or bacteriostatic water for injection to yield a reconstituted solution of approximately 100 mg/mL.

2. Shake well to dissolve and immediately withdraw a volume equal to 15 mg/kg of body mass (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.

Administer the infusion over a period of 30 minutes.

Preparation for intramuscular administration:

INVABEX must be reconstituted prior to administration.

1. Reconstitute the contents of a 1 g vial of INVABEX with 3,2 mL of 1,0 % or maximum 3,2 mL of 2,0 % lidocaine (lignocaine) hydrochloride injection*** (without adrenaline (epinephrine)). Shake vial thoroughly to form a solution. This represents the maximum recommended dose of lidocaine (lignocaine).

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: This reconstituted solution should not be administered intravenously.**

*** Refer to the professional information for lidocaine (lignocaine) hydrochloride.

Inspect parenteral products visually for particulate matter and discolouration prior to use, whenever solution and container permit. Solutions of INVABEX range from colourless to pale yellow. Variations of colour within this range do not affect the potency of the product.

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

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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