1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ERTAPENEM ASPEN 1 g sterile powder for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile powder for injection.

ERTAPENEM ASPEN is a white to yellowish powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Adults

ERTAPENEM ASPEN is indicated for the treatment of 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 pneumonia* (penicillin susceptible strains only) including cases with concurrent bacteremia, *Moraxella catarrhalis.* If Community Acquired Pneumonia is caused by *Haemophilus influenzae*, ERTAPENEM ASPEN 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.*

Adolescents and children

Safety and effectiveness of ERTAPENEM ASPEN in adolescents and children 3 months to 17 years of age are supported by evidence from adequate and well-controlled studies in adults,

pharmacokinetic data in these patients, and additional data from comparator-controlled studies in patients 3 months to 17 years of age with the following infections (see section 4.2):

- 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 ERTAPENEM ASPEN 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

Adults, adolescents and children aged 3 months and older

The dose of ERTAPENEM ASPEN in patients 13 years of age and older is 1 gram (g) given once a day.

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

Intramuscular administration of ERTAPENEM ASPEN may be used as an alternative to intravenous administration in the treatment of those infections for which intramuscular therapy is appropriate.

The usual duration of therapy with ERTAPENEM ASPEN is 3 to 14 days but varies by the type of infection and causative pathogen(s) (see section 4.1). When clinically indicated, a switch to

an appropriate oral antimicrobial may be implemented if clinical improvement has been observed.

Table 1: Dosage guideline 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[1]	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[1]	7 to 14 days[2]
Community acquired pneumonia	1 g	15 mg/kg twice daily[1]	10 to 14 days[3]
Complicated urinary tract infections including pyelonephritis	1 g	15 mg/kg twice daily[1]	10 to 14 days[3]
Acute pelvic infections including postpartum endomyometritis, septic abortion and post-surgical gynaecologic infections	1 g	15 mg/kg twice daily[1]	3 to 10 days

* Defined as creatinine clearance > 90 mL/min/1,73 m^2
1: not to exceed 1 g/day
2: patients with diabetic foot infections received up to 28 days of treatment (parenteral or parenteral plus oral switch therapy)
3: duration includes a possible switch to an appropriate oral therapy once clinical improvement has been demonstrated.

Special populations

Renal insufficiency

ERTAPENEM ASPEN may be used for the treatment of infections in adult patients with renal insufficiency. In patients whose creatinine clearance is > 30 mL/min/1,73 m^2, no dosage adjustment is necessary. Adult patients with advanced renal insufficiency (creatinine clearance ≤ 30 mL/min/1,73 m^2), including those on haemodialysis, should receive 500 mg daily. There are no data in paediatric patients with renal insufficiency.

Patients on haemodialysis

Studies have shown that 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 ERTAPENEM ASPEN within 6 hours prior to haemodialysis, a supplementary dose of 150 mg is recommended following the haemodialysis session. If ERTAPENEM ASPEN is given at least 6 hours prior to haemodialysis, no supplementary dose is needed. There are no data in patients undergoing peritoneal dialysis or haemofiltration. There are no data in paediatric patients on haemodialysis.

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

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

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

Hepatic impairment

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

Age or gender

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

Paediatric population

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

Method of administration

ERTAPENEM ASPEN may be administered by intravenous (IV) infusion or intramuscular (IM) injection. When administered intravenously, ERTAPENEM ASPEN should be infused over a period of 30 minutes.

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

4.3. Contraindications

ERTAPENEM ASPEN is contraindicated in:

- Patients with hypersensitivity to ertapenem or to any excipients in ERTAPENEM ASPEN (see section 6.1).
- Patients with hypersensitivity to other medicines in the same class (carbapenem antibacterials).
- Patients who have demonstrated anaphylactic reactions to beta-lactams (e.g. penicillins or cephalosporins).
- Patients with known bacterial meningitis. ERTAPENEM ASPEN is not recommended in the treatment of meningitis due to lack of sufficient CSF penetration.
- Patients with severe shock or heart block.

ERTAPENEM ASPEN 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, ERTAPENEM ASPEN administered intramuscularly is contraindicated in patients with a known hypersensitivity to local anaesthetics of the amide type (refer to the prescribing 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-LACTAMS INCLUDING ERTAPENEM ASPEN. 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 ERTAPENEM ASPEN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER BETA-LACTAMS AND OTHER ALLERGENS. IF AN ALLERGIC REACTION TO ERTAPENEM ASPEN 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

Seizures and other CNS adverse experiences have been reported during treatment with ERTAPENEM ASPEN (see below and section 4.8). During clinical investigations in adult patients treated with ERTAPENEM ASPEN (1 g once a day), seizures, irrespective of medicine relationship, occurred in 0,5 % of patients during study therapy plus 14 days follow-up period. These experiences have occurred most commonly in elderly patients and 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 ERTAPENEM ASPEN re-examined to determine whether it should be decreased or discontinued. See co-administration with valproic acid below and section 4.5.

Antibiotic-associated colitis

Pseudomembranous colitis (antibiotic-associated colitis) has been reported with ERTAPENEM ASPEN 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 ERTAPENEM ASPEN. Treatment with ERTAPENEM ASPEN 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. Medicines that inhibit peristalsis should not be given.

Superinfection

Prolonged use of ERTAPENEM ASPEN 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.

Valproic acid

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 ERTAPENEM ASPEN is necessary, supplemental anticonvulsant therapy should be considered (see section 4.5).

Intramuscular administration

Caution should be taken when administering ERTAPENEM ASPEN intramuscularly, to avoid inadvertent injection into a blood vessel (see section 4.2). Lidocaine (lignocaine) hydrochloride is the diluent for intramuscular administration of ERTAPENEM ASPEN. Refer to the prescribing information for lidocaine (lignocaine) hydrochloride.

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, as contained in ERTAPENEM ASPEN, concentrations and consequently to a risk of potential treatment failure. Therefore, caution should be exercised in such unusual cases.

Patients with severe infections

Experience in the use of ERTAPENEM ASPEN in the treatment of severe infections is limited. There were limited numbers of evaluable patients who were enrolled in clinical studies thus efficacy in these patients has not been established.

Community acquired pneumonia

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

Diabetic foot infections

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

Paediatric population

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.

Excipients

ERTAPENEM ASPEN contains approximately 6,0 mEq (approximately 137 mg) of sodium per 1 g dose which should be taken into consideration by patients on a controlled sodium diet (see section 6.1).

4.5. Interaction with other medicines and other forms of interaction

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. ERTAPENEM ASPEN 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). *In vitro* studies indicate that ertapenem does not inhibit P-glycoprotein-mediated transport of digoxin or vinblastine and that ertapenem is not a substrate for P-glycoprotein-mediated transport. *In vitro* studies in human liver microsomes indicate ertapenem does not inhibit metabolism mediated by any of the six major cytochrome P450 (CYP) isoforms: 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. Medicine interactions caused by inhibition of P-glycoprotein-mediated drug clearance or CYP-mediated drug clearance are unlikely (see section 5.2, Distribution and Biotransformation). No specific clinical medicine interaction studies have been conducted.

4.6. Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

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.

Breastfeeding

Ertapenem is excreted in human milk (see section 5.2, Distribution).

Because of the potential for adverse reactions on the infant, mothers should not breastfeed their infants while receiving ERTAPENEM ASPEN.

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.

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

a) Summary of the safety profile

Adult patients:

In clinical study patients who received a 1 g dose of ertapenem, most adverse event experiences reported were described as mild to moderate in severity.

Medicine related adverse experiences were reported in approximately 20 % of patients treated with ERTAPENEM ASPEN. ERTAPENEM ASPEN was discontinued due to adverse experiences thought to be medicine-related in 1,3 % of patients.

The most common medicine related adverse experiences reported during parenteral therapy in patients treated with ertapenem were diarrhoea (4,3 %), infused vein complication (3,9 %),

nausea (2,9 %) and headache (2,1 %). In adult patients the most frequently observed medicine-related laboratory abnormalities during parenteral therapy in patients receiving ERTAPENEM ASPEN 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 ERTAPENEM ASPEN were no different than those listed above.

b) Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency not known** (cannot be estimated from available data)
Infections and infestations		Fungal infections, candidiasis, pseudo-membranous enterocolitis, pneumonia, dermatomycosis, postoperative wound infection, urinary tract infection, positive *Clostridium difficile* toxin	
Blood and the lymphatic system disorders	Elevation in platelet count	Neutropenia, thrombocytopenia, decreases in white blood cells, platelet count, segmented neutrophils, haemoglobin and haematocrit; increases in eosinophils, activated partial thromboplastin time, prothrombin time, segmented neutrophils and white blood cells, decrease in lymphocytes; increases in band neutrophils, lymphocytes, metamyelocytes, monocytes, myelocytes; atypical lymphocytes	
Immune system disorders			Anaphylaxis including anaphylactoid reactions
Metabolism and nutrition disorders		Anorexia, hypoglycaemia, increases in serum glucose	

Psychiatric disorders		Confusion, agitation, anxiety, depression	Altered mental status (including aggression, delirium, disorientation, mental status changes)
Nervous system disorders	Headache,	Dizziness, somnolence, insomnia, seizure, taste perversion, tremor, syncope	 Hallucinations, depressed level of consciousness, dyskinesia, myoclonus, gait disturbance
Eye disorders		Scleral disorder	
Cardiac disorders		Sinus bradycardia, arrhythmia, tachycardia	
Vascular disorders	Infused vein complication, phlebitis/ thrombophlebitis	Extravasation, hypotension, haemorrhage, increased blood pressure	
Respiratory, thoracic and mediastinal disorders		Dyspnoea, pharyngeal discomfort, nasal congestion, cough, epistaxis, rales/rhonchi, wheezing	
Gastrointestinal disorders	Diarrhoea[2], nausea, vomiting[2]	Oral candidiasis, constipation, acid regurgitation, *C. difficile*-associated diarrhoea, dry mouth, dyspepsia, abdominal pain, dysphagia, faecal incontinence, pelvic peritonitis	Teeth staining
Hepato-biliary disorders	Elevations in ALT, AST, alkaline phosphatase	Cholecystitis, jaundice, liver disorder, increases in total serum bilirubin, direct serum bilirubin, indirect serum bilirubin	
Skin and subcutaneous tissue disorders	 Rash[2]	Erythema, pruritus, urticaria, dermatitis, desquamation	 Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome)

			Acute Generalised Exanthematous Pustulosis (AGEP),
Musculoskeletal and connective tissue disorders		Muscle cramp, shoulder pain	Muscular weakness
Renal and urinary disorders		Renal insufficiency, acute renal insufficiency, increases in serum creatinine, serum urea, decreases in serum bicarbonate, serum creatinine and serum potassium, increases in serum LDH, serum phosphorus, serum potassium Increases in urine bacteria, urine white blood cells, urine epithelial cells and urine red blood cells; urine yeast present, increase in urobilinogen	
Pregnancy, puerperium and perinatal conditions		Abortion	
Reproductive system and breast disorders	Vaginitis	Vaginal pruritus, genital bleeding	
General disorders and administrative site conditions	Infusion site erythema[1], infusion site pain[1], infusion site phlebitis[1], infusion site swelling[1]	Asthenia/fatigue, oedema/swelling, fever, pain, chest pain, malaise, infusion site induration[2], infusion site pruritis[2], infusion site warmth[2]	

1: Medicine related adverse effect reported during parenteral therapy in paediatric patients.

2: Medicine related adverse effect reported during parenteral therapy in both adult and paediatric patients.

Post-marketing adverse events:

System organ class	Frequency unknown (cannot be estimated from available data)
Immune system disorders	Anaphylaxis including anaphylactoid reactions
Psychiatric disorders	Altered mental status, agitation, aggression, delirium, disorientation, mental status changes
Nervous system disorders	Depressed level of consciousness, dyskinesia, gait disturbance. hallucinations, myclonus, tremor
Gastrointestinal disorders	Teeth staining
Skin and subcutaneous tissue disorders	Urticaria, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome)
Musculoskeletal and connective tissue disorders	Muscular weakness

c) Description of selected adverse reactions

In clinical studies, seizure was reported during parenteral therapy in 0,2 % of patients treated with ERTAPENEM ASPEN. In the majority of clinical studies, parenteral therapy was followed by a switch to an appropriate oral antimicrobial.

d) Paediatric population

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 %). In paediatric patients the most frequently observed medicine–related laboratory abnormality during parenteral therapy in patients receiving ERTAPENEM ASPEN was decreases in neutrophil count, and elevations in ALT and AST.

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 providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

Treatment

No specific information is available on the treatment of overdosage with ERTAPENEM ASPEN. In the event of overdose, ERTAPENEM ASPEN should be discontinued and general supportive care treatment given until renal elimination takes place. ERTAPENEM ASPEN 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

Category and class: A 20.1.1 Broad and medium spectrum antibiotics

Pharmacotherapeutic group: Antibacterials for systemic use, carbapenems

ATC code: J01DH03

Mechanism of action

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.*

Mechanism of resistance

For species considered susceptible to ertapenem, resistance was uncommon in surveillance studies in European territories. In resistant isolates, resistance to other antibacterial medicines 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 penicillin-binding protein (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 medicines when the mechanism is, or includes, impermeability to some compounds and/or an efflux pump.

Breakpoints

The EUCAST (European Committee on Antimicrobial Susceptibility Testing) MIC breakpoints are as follows:

•*Enterobacteriaceae: S ≤ 0,5 mg/L and R > 1 mg/L*

•*Streptococcus A,B,C,G: S ≤ 0,5 mg/L and R > 0,5 mg/L*

•*Streptococcus pneumoniae: S ≤ 0,5 mg/L and R > 0,5 mg/L*

•*Haemophilus influenzae: S ≤ 0,5 mg/L and R > 0,5 mg/L*

•*M. catarrhalis: S ≤ 0,5 mg/L and R > 0,5 mg/L*

•*Gram negative anaerobes: S ≤ 1 mg/L and R > 1 mg/L*

•*Non-species related breakpoints: S ≤ 0,5 mg/L and R > 1 mg/L*

(NB: Susceptibility of staphylococci to ertapenem is inferred from the methicillin susceptibility).

Healthcare providers should consult the local MIC breakpoints (if available).

5.2. Pharmacokinetic properties

Absorption

Ertapenem, reconstituted with 1 % lidocaine (lignocaine) 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 g or 2 g dose and IM administration of a single 1 g dose in healthy young adults are presented in Table 2.

Table 2

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 g to 2 g dose range. There is no accumulation of ertapenem in adults following multiple IV doses ranging from 0,5 g 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 3.

Table 3

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									
(15mg/kg)[1]	103,8	57,3	43,6	23,7	13,5	8,2	2,5	-	103,8
(20 mg/kg)[1]	126,8	87,6	58,7	28,4	-	12,0	3,4	0,4	126,8
(40mg/kg)[2]	199,1	144,1	95,7	58,0	-	20,2	7,7	0,6	199,1
2 to 12 years									
(15mg/kg) [1]	113,2	63,9	42,1	21,9	12,8	7,6	3,0	-	113,2
(20mg/kg) [1]	147,6	97,6	63,2	34,5	-	12,3	4,9	0,5	147,6
(40mg/kg) [2]	241,7	152,7	96,3	55,6	-	18,8	7,2	0,6	241,7
13 to 17 years									
(20mg/kg)[1]	170,4	98,3	67,8	40,4	-	16,0	7,0	1,1	170,4
(1 g)[3]	155,9	110,9	74,8	-	24,0	-	6,2	-	155,9
(40mg/kg)[2]	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. 1: up to a maximum dose of 1 g/day 2: up to a maximum dose of 2 g/day 3: 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 (see section 4.6). *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).

Biotransformation

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 or older) relative to young adults (younger than 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 a 20 mg/kg dose (up to a maximum dose of 1 g), the pharmacokinetic parameter values in patients 13 to 17 years of age were generally comparable to those in healthy young adults. Three out of six patients 13 to 17 years of age received less than a 1 g dose. To provide an estimate of the pharmacokinetic data if all patients in this age group were to receive a 1 g dose, the pharmacokinetic data were calculated adjusting for a 1 g dose, assuming linearity. A comparison of results shows that a 1 g once daily dose of ertapenem achieves a pharmacokinetic profile in patients 13 to 17 years of age comparable to that of adults. The ratios (13 to 17 years/Adults) for AUC, the end of infusion concentration and the concentration at the midpoint of the dosing interval were 0,99, 1,20, and

0,84, respectively. Plasma concentrations at the midpoint of the dosing interval following a single 15 mg/kg IV dose of ertapenem in patients 3 months to 12 years of age are comparable to plasma concentrations at the midpoint of the dosing interval following a 1 g once daily IV dose in adults (see section 5.2). 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., 30mg/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 patients (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 patients. 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 patients. 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 patients.
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 hydrogen carbonate and sodium hydroxide.

6.2. Incompatibilities

Reconstitution solutions: Sterile water for injection (WFI) and 0,9 % *w/v* Sodium chloride.

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Storage of unopened vials:

The lyophilised powder in vials should be stored at or below 25 °C.

Storage of reconstituted product:

Single dose preparation: any unused portion should be discarded. Diluted solutions should be used immediately. If not used immediately, in use storage times and conditions 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 °C to 8 °C (in a refrigerator).

Solutions should be used within 4 hours of their removal from the refrigerator.

Do not freeze solutions of ertapenem.

KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

Sterile lyophilized powder of ertapenem sodium drug substance with Sodium Hydrogen Carbonate and Sodium Hydroxide is packaged in 20 ml, colourless, clear, Type 1 glass vials with Chlorobutyl rubber injection stoppers and aluminum/lacquered flip-off overseals.

1 or 10 Vials are packed into an outer cardboard carton.

Not all packs and pack sizes are necessarily marketed.

6.6. Special precautions for disposal and other handling

Single dose preparation: any unused portion should be discarded.

Adults and adolescents 13 years of age and older *Preparation for intravenous administration*

DO NOT MIX OR CO-INFUSE ERTAPENEM ASPEN WITH OTHER MEDICINES.

DO NOT USE DILUENTS CONTAINING DEXTROSE (α-D-GLUCOSE).

ERTAPENEM ASPEN MUST BE RECONSTITUTED AND THEN DILUTED PRIOR TO ADMINISTRATION.

1. Reconstitute the contents of a 1 g vial of ERTAPENEM ASPEN 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.

Adults and adolescents 13 years of age and older

Preparation for intramuscular administration

ERTAPENEM ASPEN MUST BE RECONSTITUTED PRIOR TO ADMINISTRATION.

1. Reconstitute the contents of a 1 g vial of ERTAPENEM ASPEN with 3,2 ml of 1,0 % or maximum 3,2 ml of 2 % lidocaine (lignocaine) hydrochloride injection* (**without 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 prescribing information for lidocaine (lignocaine) hydrochloride.

Paediatric and adolescent patients 3 months to 12 years of age

Preparation for intravenous administration

DO NOT MIX OR CO-INFUSE ERTAPENEM ASPEN WITH OTHER MEDICINES.

DO NOT USE DILUENTS CONTAINING DEXTROSE (α-D-GLUCOSE).

ERTAPENEM ASPEN MUST BE RECONSTITUTED AND THEN DILUTED PRIOR TO ADMINISTRATION.

1. Reconstitute the contents of a 1 g vial of ERTAPENEM ASPEN 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.

Paediatric and adolescent patients 3 months to 12 years of age

Preparation for intramuscular administration

ERTAPENEM ASPEN MUST BE RECONSTITUTED PRIOR TO ADMINISTRATION.

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

1. 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).
2. 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 (lignocaine) hydrochloride.

Parenteral medicines should be inspected visually for particulate matter and discolouration prior to use, whenever solution and container permit. Solutions of ERTAPENEM ASPEN range from colourless to pale yellow. Variations of colour within this range do not affect the potency of the medicine.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

52/20.1.1/0443

9. DATE OF FIRST AUTHORISATION

20 October 2020

10. DATE OF REVISION OF TEXT

20 October 2020

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