PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

ABEXEM® 1 g sterile powder for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

ABEXEM 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*, ABEXEM 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 *Prevotelia bivia.*

Paediatric patients

ABEXEM 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 ABEXEM 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 ABEXEM in patients 13 years of age and older is 1 gram (g) given once a day.

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

Intramuscular administration of ABEXEM may be used as an alternative to intravenous 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 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 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

ABEXEM 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 ABEXEM within 6 hours prior to haemodialysis, a supplementary dose of 150 mg is recommended after the haemodialysis session. If ABEXEM 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 ABEXEM may be administered without regard to age (13 years of age and older) or gender.

Elderly

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

Method of administration

For instructions on the preparation of ABEXEM before administration (see section 6.6).

ABEXEM may be administered by intravenous (IV) infusion or intramuscular (IM) injection.

When administered intravenously, ABEXEM should be infused over a period of 30 minutes.

The usual duration of therapy with ABEXEM is 3 to 14 days, but it may vary according to the type and severity 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

- Hypersensitivity to ertapenem or to any of the excipients of ABEXEM (see section 6.1).
- Hypersensitivity to beta-lactam antibiotics.
- Patients with known bacterial meningitis, due to lack of sufficient cerebrospinal fluid (CSF) penetration.
- ABEXEM 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, ABEXEM 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 ABEXEM.

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

Superinfection

Prolonged use of ABEXEM 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 ABEXEM) 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 ABEXEM.

Treatment with ABEXEM 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 ABEXEM. 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 ABEXEM); 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 ABEXEM re-examined to determine whether it should be decreased or discontinued.

Encephalopathy

Encephalopathy has been reported with the use of ertapenem (see section 4.8). If ertapenem-induced encephalopathy is suspected (e.g. myoclonus, seizures, altered mental status, depressed level of consciousness), discontinuation of ertapenem as in ABEXEM 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 ABEXEM 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 ABEXEM 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 ABEXEM 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 ABEXEM for severe infections is limited.

Efficacy has not been established for the use of ABEXEM 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 ABEXEM not to inject it inadvertently into a blood vessel (see section 4.2).

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

Information on the inactive ingredients

Each vial contains approximately 6,0 millimoles of sodium (approximately 137 mg) which should be taken into consideration by patients on a controlled sodium diet.

Paediatric population

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

4.5 Interactions 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.

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 ABEXEM. The lowered valproic acid levels may lead to inadequate seizure control; therefore, concomitant use of ABEXEM 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 ABEXEM (see section 4.8). If affected, patients should be warned not to drive or operate machinery.

4.8 Undesirable effects

Tabulated list of adverse reactions

ADULTS **18 years of age and older**	
System organ class/ *Frequency*	**Adverse reactions**
Infections and infestations	
Less frequent:	Candidiasis, fungal infection, pseudomembranous enterocolitis, vaginitis, pneumonia, dermatomycosis, postoperative wound infection, urinary tract infection
Blood and lymphatic system disorders	
Less frequent:	Neutropenia, thrombocytopenia

Immune system disorders	
Less frequent:	Allergy
Frequency unknown:	Anaphylaxis including anaphylactoid reactions
Metabolism and nutrition disorders	
Less frequent:	Anorexia, hypoglycaemia
Psychiatric disorders	
Less frequent:	Insomnia, confusion, agitation, anxiety, depression
Frequency unknown:	Altered mental status (including aggression, delirium, disorientation, mental status changes)
Nervous system disorders	
Frequent:	Headache
Less frequent:	Dizziness, somnolence, taste perversion, seizure (see section 4.4), tremor, syncope
Frequency unknown:	Hallucinations, depressed level of consciousness, dyskinesia, myoclonus, gait disturbance, encephalopathy (see section 4.4)
Eye disorders	
Less frequent:	Scleral disorder
Cardiac disorders	
Less frequent:	Sinus bradycardia, dysrhythmia, tachycardia
Vascular disorders	
Frequent:	Infused vein complication, phlebitis/thrombophlebitis

Less frequent:	Hypotension, haemorrhage, increased blood pressure
Respiratory, thoracic and mediastinal disorders	
Less frequent:	Dyspnoea, pharyngeal discomfort, nasal congestion, cough, epistaxis, rales/rhonchi, wheezing
Gastrointestinal disorders	
Frequent:	Diarrhoea, nausea, vomiting
Less frequent:	Oral candidiasis, constipation, acid regurgitation, dry mouth, dyspepsia, abdominal pain, dysphagia, faecal incontinence, pelvic peritonitis, *C. difficile*-associated diarrhoea
Frequency unknown:	Stained teeth
Hepato-biliary disorders	
Less frequent:	Cholecystitis, jaundice, liver disorder
Skin and subcutaneous tissue disorders	
Frequent:	Erythema, rash, pruritus
Less frequent:	Urticaria, dermatitis, desquamation, hypersensitivity vasculitis
Frequency unknown:	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome), toxic epidermal necrolysis, Stevens-Johnson syndrome, Acute Generalised Exanthematous Pustulosis (AGEP)

Musculoskeletal and connective tissue disorders

Less frequent:	Muscle cramp, shoulder pain
Frequency unknown:	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 administration 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 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 (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

CHILDREN AND ADOLESCENTS **(3 months to 17 years of age)**	
System organ class/ *Frequency*	**Adverse reactions**
Psychiatric disorders	
Frequency unknown:	Altered mental status (including aggression)
Nervous system disorders	
Less frequent:	Headache
Frequency unknown:	Hallucinations
Vascular disorders	

Less frequent:	Hot flush, hypertension
Gastrointestinal disorders	
Frequent:	Diarrhoea, vomiting
Less frequent:	Faeces discoloured, melaena
Skin and subcutaneous tissue disorders	
Frequent:	Diaper dermatitis, rash
Less frequent:	Erythema, petechiae
General disorders and administration site conditions	
Frequent:	Infusion site pain, infusion site pruritus, infusion site erythema, infusion site swelling, infusion site phlebitis
Less frequent:	Infusion site burning, injection site erythema, infusion site warmth
Investigations	
Chemistry	
Frequent:	Elevations in ALT and AST
Haematology	
Frequent:	Decreases in neutrophil count
Less frequent:	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 providers 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 the SAHPRA website.

4.9 Overdose

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

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

ABEXEM 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: Category 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, S*tenotrophomones maltophilia.*

5.2 Pharmacokinetic properties

Absorption

Ertapenem, reconstituted with 1 % lidocaine (lignocaine) hydrochloride injection, (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 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 to 2 g dose range.

Ertapenem does not accumulate in adults after 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 h	1 h	2 h	4 h	6 h	8 h	12 h	18 h	24 h
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 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 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 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 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 to 2 hours post-dose and exceed 52 µg/ml during the period 12 to 24 hours post-dose.

Special populations

Elderly

Plasma concentrations are slightly higher in elderly adults (65 years or older) relative to young adults (younger than 65 years). In the absence of severe renal impairment, no dose adjustment is required for 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.

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 *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 (CrCl 60-90 ml/min/1,73 m^2) compared with healthy persons (ages 25 to 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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydrogen carbonate and sodium hydroxide to adjust pH to 7,5.

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

After reconstitution

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

Reconstituted intramuscular injection solution:

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

Reconstituted intravenous infusion solutions:

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 to 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 to 8 °C (in a refrigerator). Solutions should be used within 4 hours of their removal from the refrigerator. Do not freeze solutions of ABEXEM.

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

ABEXEM is supplied in 20 ml colourless clear Type I glass vials with chlorobutyl rubber stoppers and an 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 ABEXEM 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 ABEXEM 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 ABEXEM 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:

ABEXEM must be reconstituted prior to administration.

1. Reconstitute the contents of a 1 g vial of ABEXEM 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 professional information for lidocaine (lignocaine) hydrochloride.

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

Preparation for intravenous administration:

ABEXEM must be reconstituted and then diluted prior to administration.

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

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

1. Reconstitute the contents of a 1 g vial of ABEXEM with 10 ml of water for injection or 0,9 % sodium chloride injection (154 mmol/l) or bacteriostatic water for injection to yield a 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:

ABEXEM must be reconstituted prior to administration.

1. Reconstitute the contents of a 1 g vial of ABEXEM 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 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 ABEXEM 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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8. REGISTRATION NUMBER

52/20.1.1/0810

9. DATE OF AUTHORISATION / RENEWAL OF THE AUHTORISATION

Date of first authorisation: 16 March 2021

Date of renewal: 10 July 2026

10. DATE OF REVISION OF THE TEXT

06 October 2026