

# **SUMMARY OF PRODUCT CHARACTERISTICS**

## **1 NAME OF THE MEDICINAL PRODUCT**

Ertapenem 1g Powder for Concentrate for Solution for Infusion

## **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each vial contains 1.0 g ertapenem (as ertapenem sodium).

Excipient with known effect: Each vial contains approximately 6.0 mEq of sodium (approximately 137 mg).

For the full list of excipients, see section 6.1.

## **3 PHARMACEUTICAL FORM**

Powder for concentrate for solution for infusion.

White to yellowish powder.

## **4 CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Treatment

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

- Intra-abdominal infections
- Community acquired pneumonia
- Acute gynaecological infections

- Diabetic foot infections of the skin and soft tissue (see section 4.4)

#### Prevention

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

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

## 4.2 Posology and method of administration

### Posology

#### *Treatment*

- Adults and adolescents (13 to 17 years of age): The dose of Ertapenem Fresenius Kabi is 1 gram (g) given once a day by the intravenous route (see section 6.6).
- Infants and children (3 months to 12 years of age): The dose of Ertapenem Fresenius Kabi is 15 mg/kg given twice daily (not to exceed 1 g/day) by the intravenous route (see section 6.6).

### Prevention

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

#### *Paediatric population*

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

No data are available.

#### *Patients with renal impairment*

Ertapenem Fresenius Kabi may be used for the treatment of infections in adult patients with mild to moderate renal impairment. In patients whose creatinine clearance is  $> 30 \text{ ml/min/1.73 m}^2$ , no dosage adjustment is necessary. There are inadequate data on the safety and efficacy of ertapenem in patients with severe renal impairment to support a dose recommendation. Therefore, ertapenem should not be used in these patients (see section 5.2). There are no data in children and adolescents with renal impairment.

#### *Patients on haemodialysis*

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

#### *Patients with hepatic impairment*

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

#### *Elderly*

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

#### Method of administration

Intravenous administration: Ertapenem Fresenius Kabi should be infused over a period of 30 minutes.

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

Solutions of Ertapenem Fresenius Kabi range from colourless to pale yellow.

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

### **4.3 Contraindications**

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

### **4.4 Special warnings and precautions for use**

#### Hypersensitivity

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta-lactams. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. Before initiating therapy with ertapenem, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactams and other allergens (see section 4.3). If an

allergic reaction to ertapenem occurs (see section 4.8), discontinue the therapy immediately. **Serious anaphylactic reactions require immediate emergency treatment.**

#### Superinfection

Prolonged use of ertapenem may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

#### Antibiotic-associated colitis

Antibiotic-associated colitis and pseudomembranous colitis have been reported with ertapenem and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents. Discontinuation of therapy with Ertapenem and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

#### Seizures

Seizures have been reported during clinical investigation in adult patients treated with ertapenem (1 g once a day) during therapy or in the 14-day follow-up period.

Seizures occurred most commonly in elderly patients and those with pre-existing central nervous system (CNS) disorders (e.g. brain lesions or history of seizures) and/or compromised renal function. Similar observations have been made in the post-marketing environment.

#### Encephalopathy

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

#### Concomitant use with valproic acid

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

#### Sub-optimal exposure

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

#### Considerations for use in particular populations

Experience in the use of ertapenem in the treatment of severe infections is limited. In clinical studies for the treatment of community-acquired pneumonia, in adults, 25 % of evaluable patients treated with ertapenem had severe disease (defined as pneumonia severity index > III). In a clinical study for the treatment of acute gynaecologic infections, in adults, 26 % of evaluable patients treated with ertapenem had severe disease (defined as temperature  $\geq 39^{\circ}\text{C}$  and/or bacteraemia); ten patients had bacteraemia. Of evaluable patients treated with ertapenem in a clinical study for the treatment of intra-abdominal infections, in adults, 30 % had generalised peritonitis and 39 % had infections involving sites other than the appendix including the stomach, duodenum, small bowel, colon, and gallbladder; there were limited

numbers of evaluable patients who were enrolled with APACHE II scores  $\geq 15$  and efficacy in these patients has not been established.

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

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

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

#### Excipient

This medicinal product contains 137 mg sodium per vial, equivalent to 6,9% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

### **4.5 Interaction with other medicinal products and other forms of interaction**

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

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

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

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

#### Breast-feeding

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

#### Fertility

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

#### **4.7 Effects on ability to drive and use machines**

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

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

#### **4.8 Undesirable effects**

##### Summary of the safety profile

##### *Adults*

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

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

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

##### *Paediatric Population (3 months to 17 years of age):*

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

Treatment was discontinued due to adverse reactions in 0.5 % of patients.

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

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

Tabulated list of adverse reactions

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

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

	<b><i>Adults 18 years of age and older</i></b>	<b><i>Children and adolescents (3 months to 17 years of age)</i></b>
<b>Infections and infestations</b>	<p><i>Uncommon:</i> Oral candidiasis, candidiasis, fungal infection, pseudomembranous enterocolitis, vaginitis</p> <p><i>Rare:</i> Pneumonia, dermatomycosis, postoperative wound infection, urinary tract infection</p>	
<b>Blood and lymphatic system disorders</b>	<p><i>Rare:</i> Neutropenia, thrombocytopenia</p>	
<b>Immune system disorders</b>	<p><i>Rare:</i> Allergy</p> <p><i>Not known:</i> Anaphylaxis including anaphylactoid reactions</p>	
<b>Metabolism and nutrition disorders</b>	<p><i>Uncommon:</i> Anorexia</p> <p><i>Rare:</i> Hypoglycaemia</p>	
<b>Psychiatric disorders</b>	<p><i>Uncommon:</i> Insomnia, confusion</p> <p><i>Rare:</i> Agitation, anxiety, depression</p> <p><i>Not known:</i> Altered mental status (including aggression, delirium, disorientation, mental status changes)</p>	<p><i>Not known:</i> Altered mental status (including aggression)</p>
<b>Nervous system disorders</b>	<p><i>Common:</i> Headache</p> <p><i>Uncommon:</i> Dizziness, somnolence, taste perversion, seizure (see section 4.4)</p> <p><i>Rare:</i> Tremor, syncope</p>	<p><i>Uncommon:</i> Headache</p> <p><i>Not known:</i> Hallucinations</p>

	<i>Not known:</i> Hallucinations, depressed level of consciousness, dyskinesia, myoclonus, gait disturbance, encephalopathy (see section 4.4)	
<b>Eye disorders</b>	<i>Rare:</i> Scleral disorder	
<b>Cardiac disorders</b>	<i>Uncommon:</i> Sinus bradycardia  <i>Rare:</i> Arrhythmia, tachycardia	
<b>Vascular disorders</b>	<i>Common:</i> Infused vein complication, phlebitis/thrombophlebitis  <i>Uncommon:</i> Hypotension  <i>Rare:</i> Haemorrhage, increased blood pressure	<i>Uncommon:</i> Hot flush, hypertension
<b>Respiratory, thoracic and mediastinal disorders</b>	<i>Uncommon:</i> Dyspnoea, pharyngeal discomfort  <i>Rare:</i> Nasal congestion, cough, epistaxis, rales/rhonchi, wheezing	
<b>Gastrointestinal disorders</b>	<i>Common:</i> Diarrhoea, nausea, vomiting  <i>Uncommon:</i> Constipation, acid regurgitation, dry mouth, dyspepsia, abdominal pain  <i>Rare:</i> Dysphagia, faecal incontinence, pelvic peritonitis  <i>Not known:</i> teeth staining	<i>Common:</i> Diarrhoea  <i>Uncommon:</i> Faeces discoloured, melaena
<b>Hepato-biliary disorders</b>	<i>Rare:</i> Cholecystitis, jaundice, liver disorder	
<b>Skin and subcutaneous tissue disorders</b>	<i>Common:</i> Rash, pruritus  <i>Uncommon:</i> Erythema, urticaria  <i>Rare:</i> Dermatitis, desquamation, hypersensitivity vasculitis  <i>Not known:</i> Acute Generalised	<i>Common:</i> Diaper dermatitis  <i>Uncommon:</i> Erythema, rash, petechiae

	Exanthematous Pustulosis (AGEP) Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome)	
<b>Musculoskeletal and connective tissue disorders</b>	<i>Rare:</i> Muscle cramp, shoulder pain <i>Not known:</i> Muscular weakness	
<b>Renal and urinary disorders</b>	<i>Rare:</i> Renal insufficiency, acute renal insufficiency	
<b>Pregnancy, puerperium and perinatal conditions</b>	<i>Rare:</i> Abortion	
<b>Reproductive system and breast disorders</b>	<i>Rare:</i> Genital bleeding	
<b>General disorders and administration site conditions</b>	<i>Uncommon:</i> Extravasation, asthenia/fatigue, fever, oedema/swelling, chest pain <i>Rare:</i> Injection-site induration, malaise	<i>Common:</i> Infusion site pain <i>Uncommon:</i> Infusion site burning, infusion site pruritus, infusion site erythema, injection site erythema, infusion site warmth
<b>Investigations</b>		
<b>Chemistry</b>	<i>Common:</i> Elevations in ALT, AST, alkaline phosphatase <i>Uncommon:</i> Increases in total serum bilirubin, direct serum bilirubin, indirect serum bilirubin, serum creatinine, serum urea, serum glucose <i>Rare:</i> Decreases in serum bicarbonate, serum creatinine and serum potassium; increases in serum LDH, serum phosphorus, serum potassium	<i>Common:</i> Elevations in ALT and AST
<b>Haematology</b>	<i>Common:</i> Elevation in platelet count <i>Uncommon:</i> Decreases in white blood cells, platelet count, segmented neutrophils, haemoglobin and haematocrit; increases in eosinophils, activated partial thromboplastin time, prothrombin	<i>Common:</i> Decreases in neutrophil count <i>Uncommon:</i> Increases in platelet count, activated partial thromboplastin time, prothrombin time, decreases in haemoglobin

	time, segmented neutrophils and white blood cells  <i>Rare:</i> Decrease in lymphocytes; increases in band neutrophils, lymphocytes, metamyelocytes, monocytes, myelocytes; atypical lymphocytes	
<b>Urinalysis</b>	<i>Uncommon:</i> Increases in urine bacteria, urine white blood cells, urine epithelial cells and urine red blood cells; urine yeast present  <i>Rare:</i> Increase in urobilinogen	
<b>Miscellaneous</b>	<i>Uncommon:</i> Positive <i>Clostridium difficile</i> toxin	

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, Website: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

#### **4.9 Overdose**

No specific information is available on the treatment of overdose with ertapenem. Overdosing of ertapenem is unlikely. Intravenous administration of ertapenem at a 3 g daily dose for 8 days to healthy adult volunteers did not result in significant toxicity. In clinical studies in adults inadvertent administration of up to 3 g in a day did not result in clinically important adverse reactions. In paediatric clinical studies, a single intravenous (IV) dose of 40 mg/kg up to a maximum of 2 g did not result in toxicity. However, in the event of an overdose, treatment with Ertapenem should be discontinued and general supportive treatment given until renal elimination takes place.

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

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## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

#### *General properties*

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

#### Mechanism of action

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

#### Pharmacokinetic/Pharmacodynamic (PK/PD) relationship

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

#### Mechanism of resistance

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

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

Resistance is uncommon in Enterobacteriaceae and ertapenem is generally active against those with extended spectrum beta-lactamases (ESBLs). Resistance can

however be observed when ESBLs or other potent betalactamases (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 betalactamases with significant carbapenem-hydrolysing activity (e.g. IMP and VIM metallo-beta-lactamases or KPC types), though these are rare.

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

### Breakpoints

The EUCAST MIC breakpoints are as follows:

- Enterobacteriaceae:  $S \leq 0.5$  mg/l and  $R > 1$  mg/l
- Streptococcus A,B,C,G:  $S \leq 0.5$  mg/l and  $R > 0.5$  mg/l
- Streptococcus pneumoniae:  $S \leq 0.5$  mg/l and  $R > 0.5$  mg/l
- Haemophilus influenzae:  $S \leq 0.5$  mg/l and  $R > 0.5$  mg/l
- M. catarrhalis:  $S \leq 0.5$  mg/l and  $R > 0.5$  mg/l
- Gram negative anaerobes:  $S \leq 1$  mg/l and  $R > 1$  mg/l
- Non-species related breakpoints:  $S \leq 0.5$  mg/l and  $R > 1$  mg/l

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

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

### Microbiological Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. Localised clusters of infections due to carbapenem-resistant organisms have been reported in the European Union. The information below gives only approximate guidance on the probability as to whether the micro-organism will be susceptible to ertapenem or not.

<b>Commonly susceptible species:</b>
Gram-positive aerobes: Methicillin-susceptible-staphylococci (including <i>Staphylococcus aureus</i> )* <i>Streptococcus agalactiae</i> * <i>Streptococcus pneumoniae</i> *† <i>Streptococcus pyogenes</i>

Gram-negative aerobes:

*Citrobacter freundii*

*Enterobacter aerogenes*

*Enterobacter cloacae*

*Escherichia coli*\*

*Haemophilus influenzae*\*

*Haemophilus parainfluenzae*

*Klebsiella oxytoca*

*Klebsiella pneumoniae*\*

*Moraxella catarrhalis*\*

*Morganella morganii*

*Proteus mirabilis*\*

*Proteus vulgaris*

*Serratia marcescens*

Anaerobes:

*Clostridium species* (excluding *C. difficile*)\*

*Eubacterium species*\*

*Fusobacterium species*\*

*Peptostreptococcus species*\*

*Porphyromonas asaccharolytica*\*

*Prevotella species*\*

Species for which acquired resistance may be a problem:

Gram-positive aerobes:

Methicillin-resistant staphylococci + #

Anaerobes:

*Bacteroides fragilis* and species in the *B. fragilis* Group\*

Inherently resistant organisms:

Gram-positive aerobes:

*Corynebacterium jeikeium*

Enterococci including *Enterococcus faecalis* and *Enterococcus faecium*

Gram-negative aerobes:

*Aeromonas species*

*Acinetobacter species*

*Burkholderia cepacia*

<i>Pseudomonas aeruginosa</i> <i>Stenotrophomonas maltophilia</i>
Anaerobes: <i>Lactobacillus species</i>
Others: <i>Chlamydia species</i> <i>Mycoplasma species</i> <i>Rickettsia species</i> <i>Legionella species</i>

\* Activity has been satisfactorily demonstrated in clinical studies.

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

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

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

### ***Information from clinical studies***

#### Efficacy in Paediatric Studies

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

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

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

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

## 5.2 Pharmacokinetic properties

### Plasma concentrations

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

Area under the plasma concentration curve (AUC) of ertapenem in adults increases nearly dose-proportionally over the 0.5 to 2 g dose range.

There is no accumulation of ertapenem in adults following multiple intravenous doses ranging from 0.5 to 2 g daily.

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

Average plasma concentrations of ertapenem following a single 30 minute intravenous infusion of a 15 mg/kg (up to a maximum dose of 1 g) dose in patients 2 to 12 years of age were 113.2 micrograms/ml (C<sub>max</sub>) at 0.5 hour post-dose (end of infusion), 12.8 micrograms/ml at 6 hour post-dose, and 3.0 micrograms/ml at 12 hour post-dose.

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

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

### Distribution

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

The volume of distribution ( $V_{dss}$ ) of ertapenem in adults is approximately 8 litres (0.11 litre/kg) and approximately 0.2 litre/kg in paediatric patients 3 months to 12 years of age and approximately 0.16 litre/kg in paediatric patients 13 to 17 years of age.

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

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

*In-vitro* studies indicate that ertapenem does not inhibit P-glycoprotein-mediated transport of digoxin or vinblastine and that ertapenem is not a substrate for P-glycoprotein-mediated transport.

#### Biotransformation

In healthy young adults (23 to 49 years of age), after intravenous infusion of radiolabelled 1 g ertapenem, the plasma radioactivity consists predominantly (94 %) of ertapenem. The major metabolite of ertapenem is the ring-opened derivative formed by dehydropeptidase-I-mediated hydrolysis of the beta-lactam ring.

*In-vitro* studies in human liver microsomes indicate that ertapenem does not inhibit metabolism mediated by any of the six major CYP isoforms: 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4.

#### Elimination

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

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

### Special Populations

#### Gender

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

#### Elderly

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

#### Paediatric population

Plasma concentrations of ertapenem are comparable in paediatric patients 13 to 17 years of age and adults following a 1 g once daily intravenous dose.

Following the 20 mg/kg dose (up to a maximum dose of 1 g), the pharmacokinetic parameter values in patients 13 to 17 years of age were generally comparable to those in healthy young adults. To provide an estimate of the pharmacokinetic data if all patients in this age group were to receive a 1 g dose, the pharmacokinetic data were calculated adjusting for a 1 g dose, assuming linearity. A comparison of results show that a 1 g once daily dose of ertapenem achieves a pharmacokinetic profile in patients 13 to 17 years of age comparable to that of adults. The ratios (13 to 17 years/Adults) for AUC, the end of infusion concentration and the concentration at the midpoint of the dosing interval were 0.99, 1.20, and 0.84, respectively.

Plasma concentrations at the midpoint of the dosing interval following a single 15 mg/kg intravenous dose of ertapenem in patients 3 months to 12 years of age are comparable to plasma concentrations at the midpoint of the dosing interval following a 1 g once daily intravenous dose in adults (see Plasma concentrations). The plasma clearance (ml/min/kg) of ertapenem in patients 3 months to 12 years of age is approximately 2-fold higher as compared to that in adults. At the 15 mg/kg dose, the AUC value and plasma concentrations at the midpoint of the dosing interval in patients 3 months to 12 years of age were comparable to those in young healthy adults receiving a 1 g intravenous dose of ertapenem.

#### Patients with hepatic impairment

The pharmacokinetics of ertapenem in patients with hepatic impairment have not been established. Due to the limited extent of hepatic metabolism of ertapenem, its

pharmacokinetics are not expected to be affected by hepatic impairment. Therefore, no dosage adjustment is recommended in patients with hepatic impairment.

#### Patients with renal impairment

Following a single 1 g intravenous dose of ertapenem in adults, AUCs of total ertapenem (bound and unbound) and of unbound ertapenem are similar in patients with mild renal impairment (Clcr 60 to 90 ml/min/1.73 m<sup>2</sup>) compared with healthy subjects (ages 25 to 82 years). AUCs of total ertapenem and of unbound ertapenem are increased in patients with moderate renal impairment (Clcr 31 to 59 ml/min/1.73 m<sup>2</sup>) approximately 1.5-fold and 1.8-fold, respectively, compared with healthy subjects. AUCs of total ertapenem and of unbound ertapenem are increased in patients with severe renal impairment (Clcr 5 to 30 ml/min/1.73 m<sup>2</sup>) approximately 2.6-fold and 3.4-fold, respectively, compared with healthy subjects. AUCs of total ertapenem and of unbound ertapenem are increased in patients who require haemodialysis approximately 2.9-fold and 6.0-fold, respectively, between dialysis sessions, compared with healthy subjects. Following a single 1 g intravenous dose given immediately prior to a haemodialysis session, approximately 30 % of the dose is recovered in the dialysate. There are no data in paediatric patients with renal impairment.

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

### **5.3 Preclinical safety data**

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

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

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Sodium hydrogen carbonate (E500)

Sodium hydroxide (E524) to adjust pH to 7.5

## **6.2 Incompatibilities**

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

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

## **6.3 Shelf life**

2 years.

After reconstitution: Reconstituted solutions should be used immediately

After dilution: Chemical and physical in-use stability for diluted solutions (approximately 20 mg/ml ertapenem) has been demonstrated for 6 hours at 25°C or for 24 hours at 2 to 8°C (in a refrigerator). Solutions should be used within 4 hours of their removal from the refrigerator. Do not freeze solutions of Ertapenem.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times 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 (etc.) has taken place in controlled and validated aseptic conditions.

## **6.4 Special precautions for storage**

Do not store above 25°C

For storage conditions after first opening of the medicinal product, see section 6.3

## **6.5 Nature and contents of container**

20 ml colorless clear Type I glass vials with a chlorobutyl stopper and an aluminium flip-off overseal.

Supplied in packs of 10 vials.

Not all package sizes may be marketed.

## 6.6 Special precautions for disposal

Instructions for use:

For single use only.

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

### Preparation for intravenous administration:

Ertapenem Fresenius Kabi must be reconstituted and then diluted prior to administration.

### Adults and adolescents (13 to 17 years of age)

#### Reconstitution

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

#### Dilution

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

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

#### Infusion

Infuse over a period of 30 minutes.

### Children (3 months to 12 years of age)

#### Reconstitution

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

#### Dilution

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

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

### Infusion

Infuse over a period of 30 minutes.

Compatibility of Ertapenem Fresenius Kabi with intravenous solutions containing heparin sodium and potassium chloride has been demonstrated.

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

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

## **7      MARKETING AUTHORISATION HOLDER**

Fresenius Kabi Limited  
Cestrian Court, Eastgate Way,  
Manor Park, Runcorn,  
Cheshire, UK  
WA7 1NT

## **8      MARKETING AUTHORISATION NUMBER(S)**

PL 08828/0266

## **9      DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

19/04/2017 / 01/01/2021

**10 DATE OF REVISION OF THE TEXT**

27/07/2022