PRODUCT INFORMATION

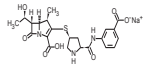
ERTAPENEM KABI Powder for Injection

a) NAME OF THE MEDICINE

Ertapenem sodium

Chemical Name: [4R-[3(3S*,5S*),4α,5β,6β(R*)]]-3-[[5-[[(3-carboxyphenyl) amino] carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0] hept-2-ene-2-carboxylic acid monosodium salt

Chemical Structure:



Molecular Formula: $C_{22}H_{24}N_3NaO_7S$

Molecular Weight: 497.497

CAS Registry No.: 153773-82-1 (ertapenem sodium)

b) DESCRIPTION

Ertapenem sodium is a white to off-white hygroscopic, weakly crystalline powder. It is soluble in water and 0.9% sodium chloride solution, practically insoluble in ethanol, and insoluble in isopropyl acetate and tetrahydrofuran. Ertapenem sodium is a 1-. methyl-carbapenem that is structurally related to beta-lactam antibiotics, such as penicillins and cephalosporins.

Ertapenem Kabi is supplied as a white to yellowish sterile lyophilized powder for intravenous (IV) infusion after reconstitution with appropriate diluent (see **DOSAGE AND ADMINISTRATION, Instructions for Use/ Handling**). Each vial contains 1.046 grams ertapenem sodium, equivalent to 1 gram ertapenem, as the active ingredient; the inactive ingredients are Sodium Hydrogen Carbonate and sodium hydroxide. The sodium content is approximately 137 mg (approximately 6.0 mEq).

c) PHARMACOLOGY

Pharmacokinetics

Absorption

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

Table 1
Plasma Concentrations of Ertapenem 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

* 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 0.5–2 g dose range.

There is no accumulation of ertapenem in adults following multiple IV doses ranging 0.5–2 g daily.

Average plasma concentrations (µg/mL) of ertapenem in paediatric patients are presented in Table 2.

Table 2
Plasma Concentrations of Ertapenem in Paediatric Patients After Single IV* Dose Administration

Age Group (Dose)	Average Plasma Concentrations (µg/mL)							
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	24 hr
3 - 23 months (15 mg/kg)†	103.8	57.3	43.6	23.7	13.5	8.2	2.5	-
(20 mg/kg)†	126.8	87.6	58.7	28.4	-	12.0	3.4	0.4
(40 mg/kg)‡	199.1	144.1	95.7	58.0	-	20.2	7.7	0.6
2 - 12 years (15 mg/kg)†	113.2	63.9	42.1	21.9	12.8	7.6	3.0	-
(20 mg/kg)†	147.6	97.6	63.2	34.5	-	12.3	4.9	0.5
(40 mg/kg)‡	241.7	152.7	96.3	55.6	-	18.8	7.2	0.6
13 - 17 years (20 mg/kg)ϒ	170.4	98.3	67.8	40.4	-	16.0	7.0	1.1
(1 g)§	155.9	110.9	74.8	-	24.0	-	6.2	-
(40 mg/kg)‡	255.0	188.7	127.9	76.2	-	31.0	15.3	2.1

* 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

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 µg/mL to approximately 85% bound at an approximate plasma concentration of 300 µg/mL.

The volume of distribution (Vdss) of ertapenem in adults is approximately 8 litres (0.11 L/kg), approximately 0.2 L/kg in paediatric patients 3 months to 12 years of age and approximately 0.16 L/kg in paediatric patients 13–17 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 are presented in Table 3. The ratio of AUC in skin blister fluid to AUC in plasma is 0.61.

Table 3
Concentrations (µg/mL) of Ertapenem in Adult Skin Blister Fluid at each Sampling Point on the Third Day of 1 g Once Daily IV Doses

0.5 hr	1 hr	2 hr	4 hr	8 hr	12 hr	24 hr
7	12	17	24	24	21	8

The level of ertapenem in breast milk of five lactating women was measured at random time points daily for five consecutive days following the last 1 g dose of IV therapy. The measured concentration of ertapenem in breast milk on the last day of therapy (5–14 days postpartum) in all five women was < 0.38 µg/mL; peak concentrations were not assessed. By Day 5 after discontinuation of therapy, the level of ertapenem was undetectable in the breast milk of four women and was detected at trace levels (< 0.13 µg/mL) in one woman.

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 ***INTERACTIONS WITH OTHER MEDICINES***).

Metabolism

In healthy young adults, after IV infusion of radiolabelled 1g 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 studies in human liver microsomes indicate that ertapenem does not inhibit metabolism mediated by any of the six major cytochrome p450 (CYP) isoforms: 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (see INTERACTIONS WITH OTHER MEDICINES).

Excretion

Ertapenem is eliminated primarily by the kidneys. The mean plasma half-life in healthy young adults and patients 13–17 years of age is approximately 4 hours and approximately 2.5 hours in paediatric patients 3 months to 12 years of age.

Following administration of a 1 g radiolabelled 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 0–2 hours post-dose and exceed 52 µg/mL during the period 12–24 hours post-dose.

Pharmacokinetics in Special Populations

Gender

Following administration of a 1 g IV dose over 30 minutes, the plasma concentrations (AUC) of ertapenem, both total and unbound, were similar in healthy male and female subjects (total drug AUC was 570.0 .g.hr/mL for men vs 566.8 .g.hr/mL for women).

Elderly

Following a 1 g IV dose of ertapenem, AUC increases by approximately 39% in elderly subjects (≥ 65 years) relative to young adults (< 65 years). No dosage adjustment is necessary in elderly patients.

Paediatric Patients

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

Following the 20 mg/kg dose (up to a maximum dose of 1 g), the pharmacokinetic parameter values in patients 13–17 years of age were generally comparable to those in healthy young adults. Three out of six patients 13–17 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 13–17 years of age comparable to that of adults. The ratios (13–17 years/ Adults) for AUC, the end of infusion concentration and the concentration at the midpoint of the dosing interval were 0.99, 1.20 and 0.84, respectively.

Plasma concentrations at the midpoint of the dosing interval following a single 15 mg/kg IV dose of ertapenem in patients 3 months 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, above). 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 Impairment

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 Impairment

Following a single 1 g IV dose of ertapenem in adults, AUC is similar in patients with mild renal insufficiency (Cl_{cr} 60–90 mL/min/1.73 m²) compared with healthy subjects (ages 25–82 years). AUC is increased in patients with moderate renal insufficiency (Cl_{cr} 31–59 mL/min/1.73 m²) approximately 1.5-fold compared with healthy subjects. AUC is increased in patients with advanced renal insufficiency (Cl_{cr} 5–30 mL/min/1.73 m²) approximately 2.6-fold compared with healthy subjects. AUC is increased in patients with end-stage renal insufficiency (Cl_{cr} < 10 mL/min/1.73 m²) approximately 2.9-fold compared with healthy subjects. Following a single 1g 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 adult patients with advanced or end-stage renal insufficiency (see **DOSAGE AND ADMINISTRATION**).

Microbiology

Ertapenem has *in vitro* activity against a wide range of gram positive and gram-negative aerobic and anaerobic bacteria. 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. Ertapenem has significant stability against hydrolysis by most classes of beta-lactamases, including penicillinases, and cephalosporinases and extended spectrum beta-lactamases, but not metallo-beta-lactamases.

Ertapenem has been shown to be active against most strains of the following microorganisms *in vitro* and in clinical infections:

Aerobic and Facultative Anaerobic Gram-Positive Microorganisms:
Staphylococcus aureus (including penicillinase-producing strains)
Streptococcus agalactiae
Streptococcus pneumoniae (penicillin susceptible isolates only)
Streptococcus pyogenes

Note: Methicillin-resistant staphylococci are resistant to ertapenem. Many strains of Enterococcus faecalis and most strains of Enterococcus faecium are resistant.

Aerobic and Facultative Anaerobic Gram-Negative Microorganisms:
Escherichia coli
Haemophilus influenzae (including beta-lactamase producing strains)
Klebsiella pneumoniae
Moraxella catarrhalis

Anaerobic Microorganisms:
Bacteroides fragilis and other species in the *B. fragilis* group
*Clostridium species (*excluding *C. difficile)*
Eubacterium species
Peptostreptococcus species
Porphyromonas asaccharolytica
Prevotella species.

The following *in vitro* data are available, **but their clinical significance is unknown**.

Ertapenem exhibits *in vitro* minimum inhibitory concentrations (MICs) of ≤ 1 µg/mL against most (≥ 90%) strains of *Streptococcus* species including *Streptococcus pneumoniae*, ≤ 0.5 µg/mL against most (≥ 90%) strains of *Haemophilus* species, ≤ 2 µg/mL against most (≥ 90%) strains of the other aerobic and facultative anaerobic microorganisms and ≤ 4 µg/mL against most (≥ 90%) strains of the strict anaerobic microorganisms in the following list; however, the safety and effectiveness of ertapenem in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical studies:

Aerobic and Facultative Anaerobic Gram-Positive Microorganisms:
Staphylococcus species, coagulase negative, methicillin susceptible
Streptococcus pneumoniae, (penicillin resistant - intermediate isolates only)

Note: Methicillin-resistant staphylococci are resistant to ertapenem. Many strains of *Enterococcus faecalis* and most strains of *Enterococcus faecium* are resistant.

Aerobic and Facultative Anaerobic Gram-Negative Microorganisms:
Citrobacter freundii
Enterobacter aerogenes
Enterobacter cloacae
Haemophilus parainfluenzae
Klebsiella oxytoca (excluding ESBL producing isolates)
Klebsiella pneumoniae producing ESBLs
Morganella morganii
Proteus vulgaris
Serratia marcescens

Anaerobic Microorganisms:
Fusobacterium species.

INDICATIONS

Ertapenem is indicated for the treatment of patients with moderate to severe infections caused by susceptible strains of microorganisms, as well as initial empiric therapy prior to the identification of causative organisms in the infections listed below:

- Complicated Intra-Abdominal Infections
- Complicated Skin and Skin Structure Infections including diabetic lower extremity infections
- Community Acquired Pneumonia
- Complicated Urinary Tract Infections including pyelonephritis
- Acute Pelvic Infections including postpartum endomyometritis, septic abortion and post surgical gynecologic infections

To reduce the development of drug-resistant bacteria and maintain effectiveness of Ertapenem and other antibacterial drugs, Ertapenem should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Ertapenem Kabi is contraindicated in patients with known hypersensitivity to any component of this product or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to beta-lactams.

PRECAUTIONS

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 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 generally not recommended. Anti-bacterials 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 is necessary, supplemental anti-convulsant therapy should be considered (See DRUG INTERACTIONS).

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.

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. 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, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactams and other allergens. If an allergic reaction to ertapenem occurs, discontinue the drug immediately. **Serious anaphylactic reactions require immediate emergency treatment.**

As with other antibiotics, 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.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ertapenem. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with ertapenem use (this may occur up to several weeks after cessation of antibiotic therapy).

[1] Acute pelvic infection is not the same entity as pelvic inflammatory disease

Mild cases usually respond to drug discontinuation alone. In moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluid, electrolytes and protein replacement should be provided when indicated.

Seizure and other central nervous system (CNS) adverse experiences have been reported during treatment with ertapenem (see **ADVERSE EFFECTS**). During clinical investigations in adult patients treated with ertapenem (1 g once a day), seizures, irrespective of drug relationship, occurred in 0.5% of patients during study therapy plus 14-day follow-up period. These experiences have occurred most commonly in patients with CNS disorders (e.g. brain lesions or history of seizures) and/or compromised renal function. Close adherence to the recommended dosage regimen is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus or seizures occur, patients should be evaluated neurologically and the dosage of ertapenem re-examined to determine whether it should be decreased or discontinued.

Use in CNS Infections

Ertapenem is not recommended in the treatment of meningitis or other CNS infections in the paediatric population due to a lack of sufficient CSF penetration to cover all relevant pathogens.

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Effects of Fertility

Ertapenem had no adverse effect on fertility of either male or female rats at doses up to 700 mg/kg/day IV, which was associated with a plasma AUC level similar to the anticipated human value at the clinically recommended dose.

Use in Pregnancy

(Category B3)

In mice and rats given IV doses of up to 700 mg/kg/day (for rats, similar to human exposure at the recommended dose of 1 g based on plasma AUCs; no exposure data were available for mice), there was no evidence of developmental toxicity as assessed by external, visceral and skeletal examination of the fetuses. However, in mice given 700 mg/kg/day, slight decreases in average fetal weights, and an associated decrease in the average number of ossified sacrocaudal vertebrae, were observed. Ertapenem crosses the placental barrier in rats.

There are no adequate and well-controlled studies in pregnant women. Ertapenem should not be used in pregnant women, unless the expected therapeutic benefit to the mother clearly outweighs the potential risk to the mother and fetus.

Use in Lactation

Ertapenem is excreted in human milk (see **PHARMACOLOGY, Pharmacokinetics**, Distribution). In rats given IV doses of up to 700 mg/kg/day (similar to human exposure at the recommended dose of 1g based on plasma AUCs) there was no evidence of post-natal toxicity. Ertapenem should not be used in a breastfeeding woman, unless the expected therapeutic benefit to the mother clearly outweighs the potential risk to the infant.

Paediatric Use

Safety and effectiveness of ertapenem in paediatric patients 3 months to 17 years of age are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in paediatric patients and additional data from comparator-controlled studies in paediatric patients 3 months to 17 years of age and 2–17 years of age in intra-abdominal infection and acute pelvic infection[1] comparator-controlled studies (see **INDICATIONS** and **Paediatric Patients**). There are no data in paediatric patients with renal insufficiency.

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

Use in Elderly

In clinical studies, the efficacy and safety of ertapenem in the elderly (≥ 65 years) was comparable to that seen in younger patients (< 65 years).

Genotoxicity

Ertapenem was not genotoxic, as assessed in vitro for gene mutations, chromosomal aberrations and DNA strand breaks in cultured mammalian cells. An in vivo assay of chromosomal damage (micronucleus test in mice) was also negative.

Carcinogenicity
The carcinogenic potential of ertapenem has not been examined in long term animal studies.

Effects on Ability to Drive and Operate Machinery
Dizziness and somnolence can occur which may affect some patients' ability to drive and/or operate machinery.

INTERACTION WITH OTHER MEDICINES
When ertapenem is administered with probenecid, probenecid competes for active tubular secretion and thus inhibits the renal excretion of ertapenem. This leads to small but statistically significant increases in the elimination half-life (19%) and in the AUC (25%). No dosage adjustment is necessary when ertapenem is given with probenecid. Because of the small effect on half-life, the co-administration with probenecid to extend the half-life of ertapenem is not recommended.

In vitro studies indicate that ertapenem does not inhibit P-glycoprotein-mediated transport of digoxin or vinblastine and that ertapenem is not a substrate for P-glycoprotein-mediated transport. In vitro studies in human liver microsomes indicate ertapenem does not inhibit metabolism mediated by any of the six major cytochrome p450 (CYP) isoforms: 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. Drug interactions caused by inhibition of P-glycoprotein-mediated drug clearance or CYP-mediated drug clearance are unlikely (see **PHARMACOLOGY, Pharmacokinetics,** Distribution and Metabolism).

Other than with probenecid, no specific clinical drug interaction studies have been conducted.

The concomitant use of ertapenem and valproic acid/semisodium valproate is generally not recommended. Anti-bacterials other than carbapenems should be considered to treat infections in patients whose seizures are well controlled on valproic acid or semisodium valproate. If administration of ertapenem is necessary, supplemental anti- convulsant therapy should be considered.

Case reports in the literature have shown that co-administration of carbapenems, including ertapenem, to patients receiving valproic acid or semisodium valproate results in a reduction of 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 semisodium valproate may not be sufficient to overcome this interaction. Although the mechanism of this interaction is unknown, data from in vitro and animal studies suggest that carbapenems may inhibit the hydrolysis of valproic acid's glucuronide metabolite (VPA-g) back to valproic acid, thus decreasing the serum concentrations of valproic acid.

ADVERSE EFFECTS
Adult Patients
The total number of patients treated with ertapenem in clinical studies was over 1,900 of which over 1,850 received a 1 g dose of ertapenem. Most adverse experiences reported in these clinical studies were described as mild to moderate in severity. Drug-related adverse experiences were reported in approximately 20% of patients treated with ertapenem. Ertapenem was discontinued due to adverse experiences thought to be drug-related in 1.3% of patients.

The most common drug-related adverse experiences reported during parenteral therapy in patients treated with ertapenem were diarrhoea (4.3%), infused vein complication (3.9%), nausea (2.9%) and headache (2.1%).

The following drug-related adverse experiences were reported during parenteral therapy in ≥ 1.0% of patients treated with ertapenem:

Table 9
Incidence (%) of Drug-Related Adverse Experiences* Reported During Parenteral Therapy in ≥ 1.0% of Patients Treated with Ertapenem in Clinical Studies

Adverse Events	Ertapenem 1 g daily (n = 1,866)	Piperacillin/ Tazobactam 3.375 g q6h (n = 775)	Ceftriaxone 1 or 2 g daily (n = 912)
Local			
Infused vein complication	3.9	5.5	4.3
Phlebitis/ thrombophlebitis	1.3	1.3	1.4
Systemic			
Diarrhoea	4.3	6.6	3.7
Nausea	2.9	3.2	2.6
Headache	2.1	1.0	2.2
Vomiting	1.0	1.5	0.9

* determined by the investigator to be possibly, probably or definitely drug-related

Additional drug-related adverse experiences that were reported during parenteral therapy with ertapenem with an incidence > 0.1% but < 1.0% within each body system are listed below.

Body as a Whole: asthenia/fatigue, candidiasis, oedema/ swelling, fever, pain, abdominal pain, chest pain
Cardiovascular System: extravasation, hypotension, bradycardia
Digestive System: acid regurgitation, anorexia, oral candidiasis, constipation, C. difficile-associated diarrhoea, dry mouth, dyspepsia
Nervous System & Psychiatric: confusion, dizziness, insomnia, somnolence
Respiratory System: dyspnoea
Skin & Skin Appendage: erythema, pruritus Special Senses: taste perversion
Urogenital System: vaginal pruritus.

In clinical studies, seizure was reported during parenteral therapy in 0.2% of patients treated with ertapenem, 0.3% of patients treated with piperacillin/ tazobactam and 0% of patients treated with ceftriaxone.

In the majority of clinical studies, parenteral therapy was followed by a switch to an appropriate oral antimicrobial. During the entire treatment period and a 14-day post-treatment follow-up period, drug-related adverse experiences in patients treated with ertapenem included those listed above as well as rash and vaginitis at an incidence of ≥ 1.0% (common) and allergic reactions, malaise and fungal infections at an incidence of > 0.1% but < 1.0% (uncommon).

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

In a clinical study for the treatment of diabetic foot infections in which 289 adult diabetic patients were treated with ertapenem, the drug-related adverse experience profile was generally similar to that seen in previous clinical trials.

Paediatric Patients
Clinical studies enrolled 384 paediatric patients treated with ertapenem. The overall adverse experience profile is comparable to that in adult patients. Table 10 shows the incidence of drug-related adverse experiences reported during parenteral therapy in ≥ 1.0% of paediatric patients in these studies.

Table 10
Incidence (%) of Drug-Related Adverse Experiences* Reported During Parenteral Therapy in ≥ 1.0% of Paediatric Patients Treated with Ertapenem in Clinical Studies

Adverse Events	Ertapenem (n = 384)	Ceftriaxone (n = 100)	Ticarcillin/ clavulanate (n = 24)
Local			
Infusion site erythema	2.6	2.0	0.0
Infusion site pain	5.5	1.0	12.5
Infusion site phlebitis	1.8	3.0	0.0
Infusion site swelling	1.0	0.0	0.0
Systemic			
Diarrhoea	5.5	10.0	4.2
Rash	1.3	1.0	4.2
Vomiting	1.6	2.0	0.0

* determined by the investigator to be possibly, probably, or definitely drug-related

In the paediatric clinical studies, the majority of the patients had parenteral therapy followed by a switch to an appropriate oral antimicrobial. During the entire treatment period and a 14-day post-treatment follow-up period, drug-related adverse experiences reported with an incidence of ≥ 1.0% in patients treated with ertapenem were no different than those listed in Table 10.

Additional drug-related adverse experiences that were reported during parenteral therapy with ertapenem with an incidence > 0.5% but < 1.0% within each body system are listed below.

General disorders and administration site conditions: infusion site induration, infusion site pruritus, infusion site warmth

Vascular disorders: phlebitis.

Post-Marketing Experience
The following post-marketing adverse experiences have been reported.

Immune System: anaphylaxis including anaphylactoid reactions
Psychiatric disorders: altered mental status (including agitation, aggression, delirium, disorientation, mental status changes)
Nervous System disorders: depressed level of consciousness, dyskinesia, gait disturbance, hallucinations, myoclonus, tremor. Seizures (very rare). Seizures occurred most frequently in elderly patients and those with pre-existing CNS disorders (e.g. brain lesions or history of seizures) and/or compromised renal function (see PRECAUTIONS).
Gastrointestinal disorders: teeth staining
Skin & Subcutaneous Tissue disorders: urticaria, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome)
Musculoskeletal & Connective Tissue disorders: muscular weakness.

Laboratory Tests
Adult Patients
Clinically Significant Laboratory Abnormalities that were measured during parenteral therapy in ≥ 1.0% of patients treated with ertapenem in clinical studies are presented in Table 11.

Table 11
Incidence (%) of Clinically Significant Laboratory Abnormalities (CLSA) Reported During Parenteral Therapy in ≥ 1.0% of Patients Treated with Ertapenem in Clinical Studies

Laboratory Test (CLSA Criteria)	Ertapenem 1 g daily (n[†‡] = 1,866)	Piperacillin/ Tazobactam 3.375 g q6h (n[†] = 775)	Ceftriaxone 1 or 2 g daily (n[§§] = 912)
Absolute Neutrophil Count (< 1,800 cells/µL)	3.0	1.4	1.9
ALT (> 2.5× ULN)	4.8	3.0	5.7
AST (> 2.5× ULN)	5.5	4.5	4.2
Direct Serum Bilirubin (>2.5× ULN)	3.2	4.3	0.8
Haematocrit (< 24%)	2.7	3.5	1.4
Haemoglobin (< 8 g/dL)	3.1	3.8	0.9
Platelet Count (< 75,000 cells/µL)	1.2	1.0	1.1
Serum Alkaline Phosphatase (> 2.5× ULN)	2.4	2.6	1.7
Serum Creatinine (> 1.5× ULN)	1.3	2.8	1.5
Total Serum Bilirubin (> 2.5× ULN)	1.1	1.2	0.4

† includes adult patients with renal dose adjustments
‡ includes adult patients randomised to 1 g but dose adjusted to 2 g
§ includes adult patients who also received metronidazole
n = the total number of treated patients in the treatment group
ULN = Upper Limit of Normal range

The most frequently observed drug-related laboratory abnormalities during parenteral therapy in patients receiving ertapenem 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, drug-related laboratory abnormalities in patients treated with ertapenem were no different than those listed above.

Other drug-related laboratory abnormalities included the following: increases in direct serum bilirubin, total serum bilirubin, eosinophils, indirect serum bilirubin, PTT, urine bacteria, BUN, serum creatinine, serum glucose, monocytes, urine epithelial cells, urine red blood cells; decreases in segmented neutrophils, white blood cells, haematocrit, haemoglobin and platelet count.

In a clinical study for the treatment of diabetic foot infections in which 289 adult diabetic patients were treated with ertapenem, the drug related laboratory adverse experience profile was generally similar to that seen with previous clinical trials.

Paediatric Patients
The overall laboratory adverse experience profile is comparable to that in adults. Table 12 shows the incidence of laboratory adverse experiences reported in ≥ 1.0% of paediatric patients in clinical studies.

Table 12
Incidence* (%) of Specific Drug-Related Laboratory Adverse Experiences Reported During Parenteral Therapy in ≥ 1.0% of Paediatric Patients Treated with Ertapenem in Clinical Studies

Laboratory adverse experiences	Ertapenem (n† = 384)	Ceftriaxone (n† =100)	Ticarcillin/ clavulanate (n† =24)
ALT ↑	1.9	0.0	4.3
AST ↑	1.9	0.0	4.3
Neutrophil Count ↓	2.5	1.1	0.0

* number of patients with laboratory adverse experiences/number of patients with the laboratory test; where at least 300 patients had the test
† number of patients with one or more laboratory tests

Additional drug-related laboratory adverse experiences that were reported during parenteral therapy in > 0.5% but < 1.0% of paediatric patients treated with ertapenem in clinical studies include: increase in eosinophils.

Other drug-related laboratory abnormalities during the entire treatment period plus 14-day follow-up included the following: elevations in ALT, elevations in AST, decreases in white blood cells.

DOSAGE AND ADMINISTRATION
The usual dose of ertapenem in patients 13 years of age and older is 1 g given once a day. The usual dose of ertapenem in patients 3 months to 12 years of age is 15 mg/kg twice daily (not to exceed 1 g/day).

Ertapenem Kabi is administered by IV infusion over a period of 30 minutes.

The usual duration of therapy with ertapenem is 3–14 days, but varies by the type of infection and causative pathogen(s) (see **INDICATIONS**). When clinically indicated, a switch to an appropriate oral antimicrobial may be implemented if clinical improvement has been observed.

In controlled clinical studies, patients were treated 3–14 days. Total treatment duration was determined by the treating physician based on site and severity of the infection, and on the patient's clinical response. In some studies, treatment was converted to oral therapy at the discretion of the treating physician after clinical improvement had been demonstrated.

Patients with Renal Insufficiency
Ertapenem 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 m², no dosage adjustment is necessary. Adult patients with advanced renal insufficiency (creatinine clearance ≤30 mL/min/1.73 m²), including those on haemodialysis, should receive 500 mg daily. There are no data in paediatric patients with renal insufficiency.

Patients on Haemodialysis
In a clinical study in adults, 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 patients on haemodialysis are given the recommended daily dose of 500 mg of ertapenem within 6 hours prior to haemodialysis, a supplementary dose of 150 mg is recommended following the haemodialysis session. If ertapenem is given at least 6 hours prior to haemodialysis, no supplementary dose is needed. There are no data in paediatric patients undergoing haemodialysis. There are no data in adult and paediatric patients undergoing peritoneal dialysis or haemofiltration.

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

Males: $\frac{\text{(weight in kg)} \times (140 - \text{age in years})}{\text{serum creatinine (micromol/L)}} \times 1.2$

Females: 0.85 × value calculated for males

No dosage adjustment is recommended in patients with impaired hepatic function (see **PHARMACOLOGY, Pharmacokinetics**, Pharmacokinetics in Special Populations, *Hepatic Impairment)*.

In patients 13 years of age and older, the recommended dose of ertapenem can be administered without regard to age or gender.

Instructions for Use/Handling
Preparation for IV Administration

DO NOT MIX OR CO-INFUSE ERTAPENEM KABI WITH OTHER MEDICATIONS, OTHER THAN HEPARIN OR POTASSIUM CHLORIDE.

DO NOT USE DILUENTS CONTAINING GLUCOSE.

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

Patients 13 years of age and older
1. Reconstitute the contents of a 1 g vial of Ertapenem Kabi with 10 mL of one of the following:Water for Injections or 0.9% Sodium Chloride Injection or Bacteriostatic Water for Injections.
2. Shake well to dissolve and immediately transfer the contents of the reconstituted vial to 50 mL of 0.9% Sodium Chloride Injection. The resulting solution is chemically and physically stable only if used within 6 hours at room temperature, or stored for 24 hours at 2–8°C and used within 4 hours after removal from refrigeration.
3. To ensure adequate potency and to avoid microbiological hazard, the ertapenem solution should be used as soon as practicable after reconstitution and further dilution. If storage is unavoidable, the solution should be held at 2–8°C for not more than 24 hours, and used as soon as practicable within 4 hours after removal from refrigeration. The solution should not be frozen.
4. The solution should be infused over a period of 30 minutes.

Paediatric patients 3 months to 12 years of age
1. Reconstitute the contents of a 1 g vial of Ertapenem Kabi with 10 mL of one of the following:Water for Injections or 0.9% Sodium Chloride Injection or Bacteriostatic Water for Injections.
2. Shake well to dissolve and immediately withdraw a volume equal to 15 mg/kg of body weight and dilute in 0.9% Sodium Chloride Injection to a final concentration of 20 mg/mL or less. The resulting solution is chemically and physically stable only if used within 6 hours at room temperature, or stored for 24 hours at 2–8°C and used within 4 hours after removal from refrigeration.
3. To ensure adequate potency and to avoid microbiological hazard, the ertapenem solution should be used as soon as practicable after reconstitution and further dilution. If storage is unavoidable, the solution should be held at 2–8° C for not more than 24 hours, and used as soon as practicable within 4 hours after removal from refrigeration. The solution should not be frozen.
4. The solution should be infused over a period of 30 minutes.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to use, whenever solution and container permit. Solutions of Ertapenem Kabi range from colourless to pale yellow. Variations of colour within this range do not affect the potency of the product.

Product is for single use in one patient only. Discard any residue.

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

OVERDOSAGE
No specific information is available on the treatment of overdosage with ertapenem. Intentional 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 experiences. In paediatric clinical studies, a single IV dose of 40 mg/kg up to a maximum of 2 g did not result in toxicity.

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

Ertapenem can be removed by haemodialysis; however, no information is available on the use of haemodialysis to treat overdosage.

PRESENTATION AND STORAGE CONDITIONS
Each vial of unreconstituted Ertapenem Kabi contains a white to yellowish powder containing 1 g ertapenem (as sodium).

Vials (Type I clear, colourless glass, chlorobutyl rubber stopper, aluminium cap): packs of 1s and 10s.

Not all presentations may be available locally.

Storage
Store below 25°C.

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DATE OF LAST REVISION:
August 2020

FRESENIUS KABI