SUMMARY OF RPODUCT CHARACTERISTICS

1. 1. NAME OF THE MEDICINAL PRODUCT

Ertapenem-TF, 1000 mg, lyophilisate for concentrate for solution for infusion.
International nonproprietary name: Ertapenem.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Ertapenem

2.2 Qualitative and quantitative composition

One vial contains:

Active substance:	
ertapenem (as ertapenem sodium)	1000 mg
excipients:	sodium bicarbonate, sodium hydroxide

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilisate for concentrate for solution for infusion 1000 mg.
Powder from white to yellowish color.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment

Treatment of infections caused by microorganisms sensitive to ertapenem, when parenteral therapy is required in adults and children from 3 months of age (see sections 4.4 and 5.1):

- Treatment of intra-abdominal infections;
- Treatment of community-acquired pneumonia;
- Treatment of acute infections in gynecology;
- Treatment of skin and soft tissue infections in diabetic foot syndrome (see section 4.4).

Prevention

Ertapenem-TF is indicated for the prevention of surgical site infection following elective colorectal surgery in adult patients (see section 4.4).
Official guidelines for the appropriate use of antibacterial agents shall be taken into account.

4.2 Posology and method of administration

Posology

Treatment

Adults and adolescents (13 to 17 years of age). The recommended dose of Ertapenem-TF is 1000 mg intravenously once daily.
Infants and children (3 months to 12 years of age). The recommended dose of Ertapenem-TF is 15 mg/kg twice daily (not to exceed 1000 mg/day).

Prevention

Adults. For the prevention of surgical site infections following elective colorectal surgery, the recommended dose is 1000 mg; the infusion shall be stopped 1 hour before the start of surgery.
The usual duration of treatment with Ertapenem-TF is 3 to 14 days, but may vary depending on the type and severity of infection and the pathogen(s). If clinically indicated, oral antibiotics may be switched to when clinical improvement occurs.

Special populations

Renal impairment

Ertapenem-TF can be used to treat infections in adult patients with mild to moderate renal impairment. No dose adjustment is necessary in patients with creatinine clearance > 30

ml/min/1.73 m^2. There are insufficient data on the safety and efficacy of ertapenem in patients with severe renal impairment to make dosage recommendations. Therefore, ertapenem shall not be used in these patients (see section 5.2). No data are available in children and adolescents with renal impairment.

Hemodialysis

There are insufficient data on the safety and efficacy of ertapenem in patients undergoing hemodialysis to make dosing recommendations. Therefore, ertapenem shall not be used in these patients.

Hepatic impairment

No dosage adjustment is necessary for patients with hepatic impairment (see section 5.2).

Elderly

The recommended dose of Ertapenem-TF shall be used, except in cases of severe renal impairment (see subsection "Renal impairment").

Pediatric population

The safety and efficacy of ertapenem in children under 3 months of age have not been established. No data available.

Method of administration

Ertapenem-TF is administered intravenously.

Ertapenem-TF shall be administered as an infusion over 30 minutes.

Information on the preparation of the solution is provided in section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients (see section 6.1).
- Hypersensitivity to any of the carbapenem antibiotics.
- Severe hypersensitivity reaction (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibiotics (e.g. penicillins or cephalosporins).
- Children under 3 months of age.

4.4 Special warnings and precautions for use

Hypersensitivity

Serious and sometimes fatal hypersensitivity (anaphylactic) reactions have been reported in patients treated with beta-lactam antibiotics. Patients with a history of hypersensitivity to various allergens are more likely to experience such reactions. Before initiating treatment with ertapenem, the patient shall be carefully questioned about previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactam antibiotics and other allergens (see section 4.3). If an allergic reaction to ertapenem occurs (see section 4.8), treatment shall be discontinued immediately. **Serious anaphylactic reactions require immediate emergency treatment.**

Superinfection

Long-term use of ertapenem may result in overgrowth of insensitive organisms. The patient shall be re-evaluated. If superinfection occurs during treatment, appropriate treatment shall be instituted.

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 with diarrhea following the use of antibacterial medicinal products. Discontinuation of Ertapenem-TF and initiation of specific treatment for *Clostridium difficile* shall be considered. Medicinal products that suppress intestinal motility shall not be administered.

Seizures

Seizures have been reported in clinical trials in adult patients during treatment with ertapenem (1000 mg daily) or for 14 consecutive days. Seizures were observed most frequently in elderly

patients and in patients with pre-existing central nervous system disorders (patients with brain damage or seizures) and/or renal impairment. Similar cases have also been reported in post-marketing surveillance.

Concomitant use with valproic acid

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

Suboptimal exposure

Based on the available data, it cannot be excluded that in rare cases of surgical interventions lasting more than 4 hours, patients who have received ertapenem in suboptimal concentrations may be at risk for potential treatment failure. Therefore, caution shall be exercised in such rare cases.

Excipients

This medicinal product contains approximately 6.0 mEq (approximately 137 mg) sodium per 1.0 g dose, which shall be taken into account when treating patients on a controlled sodium diet.

Consideration of use of the medicinal product in special population

Experience with ertapenem in the treatment of severe infections is limited. In clinical trials of community-acquired pneumonia (adults), 25% of patients receiving ertapenem had severe disease (defined as pneumonia severity index > III). In a clinical trial of acute gynecologic infections (adults), 26% of patients receiving ertapenem had severe disease (temperature ≥ 39°C and/or bacteremia); 10 patients had bacteremia. In a clinical trial of intra-abdominal infections (in adults), 30% of patients receiving ertapenem had generalized peritonitis and 39% had other GI infections (excluding appendicitis), including gastric, duodenal, small bowel, colonic, and gallbladder infections; there were a limited number of patients enrolled in the trial with an APACHE II score ≥ 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.

The efficacy of ertapenem in the treatment of diabetic foot infection and associated osteomyelitis has not been established.

There is relatively limited experience with the use of ertapenem in children under 2 years of age. In this population, particular attention shall be paid to determining the susceptibility of the infecting microorganism(s) to ertapenem. No data are available for children under 3 months of age.

4.5 Interaction with other medicinal products and other forms of interaction

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

When valproic acid and carbapenems are co-administered, decreased valproic acid levels have been reported, which may fall below the therapeutic range. Decreased valproic acid levels may result in inadequate seizure control, therefore co-administration of ertapenem and valproic acid/sodium valproate is not recommended and an alternative antibiotic or anticonvulsant shall be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo-fetal development, parturition or postnatal development. However, ertapenem shall not be used during pregnancy unless the potential benefit outweighs the possible risk to the fetus.

Lactation

Ertapenem is secreted into breast milk. Since there is a potential for adverse reactions in the child, women shall not breast-feed during treatment with ertapenem.

Fertility

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

4.7 Effects on ability to drive and use machines

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

Ertapenem may affect the patient's ability to drive and use machines. Patients shall be aware that dizziness and drowsiness have been reported with ertapenem (see section 4.8).

4.8 Adverse reactions

General description of the safety profile

Adults

The total number of patients treated with ertapenem in clinical trials was more than 2,200, of whom more than 2,150 patients received ertapenem 1000 mg. Adverse reactions (those 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 1000 mg dose prior to surgery in a clinical trial for the prevention of postoperative wound infection after colorectal surgery.

In patients receiving ertapenem alone, the most frequently reported adverse reactions during treatment and for 14 days after treatment discontinuation were diarrhea (4.8%), venous infusion complications (4.5%), and nausea (2.8%).

In patients receiving ertapenem alone, the most frequently reported laboratory abnormalities during treatment and for 14 days after stopping treatment were increased ALT (4.6%), AST (4.6%), alkaline phosphatase (3.8%), and platelet count (3.0%).

Pediatric population (3 months to 17 years of age)

A total of 384 patients were treated with ertapenem in clinical studies. The overall safety profile was consistent with that seen in adults. Adverse reactions (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.

In patients receiving ertapenem alone, the most commonly reported adverse reactions during treatment and for 14 days after discontinuing treatment were: diarrhea (5.2%), infusion site pain (6.1%).

In patients receiving ertapenem alone, the most commonly reported laboratory abnormalities occurring during treatment and for 14 days after discontinuing treatment were: neutrophil count decreased (3.0%), ALT increased (2.9%), and AST increased (2.8%). In patients receiving ertapenem alone, the following adverse reactions were reported during treatment and for 14 days after discontinuation of treatment with a frequency of: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), not known (frequency cannot be estimated from the available data).

	Adults aged 18 years and over	*Children and adolescents (from 3 months to 17 years)*
infections and infestations	*Uncommon* - oral candidiasis, candidiasis, fungal infection, pseudomembranous enterocolitis, vaginitis. *Rare* - pneumonia, dermatomycosis,	

	Adults aged 18 years and over	*Children and adolescents (from 3 months to 17 years)*
	postoperative wound infection, urinary tract infection.	
Blood and lymphatic system disorders	*Rare* – neutropenia, thrombocytopenia.	
Immune system disorders	*Rare* – allergy. *Frequency unknown* – anaphylaxis, including anaphylactoid reactions.	
Metabolism and nutrition disorders	*Uncommon* – anorexia. *Rare* – hypoglycemia.	
Psychiatric disorders	*Uncommon* - insomnia, confusion. *Rare* - agitation, anxiety, depression. *Frequency unknown* - mental status disorders (including aggression, delirium, disorientation, changes in mental status).	*Frequency unknown* - mental disorders (including aggression).
Nervous system disorders	*Common* - headache. *Uncommon* - dizziness, drowsiness, taste changes, convulsions (see section 4.4). *Rare* - tremor, syncope. *Frequency unknown* - hallucinations, decreased level of consciousness, gait disturbance, dyskinesia, myoclonus.	*Uncommon* - headache. *Frequency unknown* - hallucinations.
Eye disorders	*Rare* – pathological changes in the sclera.	
Cardiac disorders	*Uncommon* – sinus bradycardia. *Rare* – arrhythmia, tachycardia.	
Vascular disorders	*Common* - venous complication at the infusion site, phlebitis/thrombophlebitis. *Uncommon* - arterial hypotension. *Rare* - bleeding, increased blood pressure.	*Uncommon* – hot flashes, arterial hypertension.
Respiratory, thoracic and mediastinal disorders	*Uncommon* - dyspnea, discomfort in the throat. *Rare* - nasal congestion, cough, nosebleed, wheezing/dry rales, hissing respiration.	

	Adults aged 18 years and over	*Children and adolescents (from 3 months to 17 years)*
Gastrointestinal disorders	*Common* - diarrhea, nausea, vomiting. *Uncommon* - constipation, acid regurgitation, dry mouth, dyspepsia, abdominal pain. *Rare* - dysphagia, fecal incontinence, pelvic peritonitis. Frequency unknown - teeth staining.	*Common* – diarrhea. *Uncommon* - change in stool color, melena.
Hepatobiliary disorders	*Rare* - cholecystitis, jaundice, liver disorders.	
Skin and subcutaneous tissue disorders	*Common* - rash, itching. *Uncommon* - erythema, urticaria. *Rare* - dermatitis, desquamation. *Frequency unknown* - acute generalized exanthematous pustulosis, drug rash, accompanied by eosinophilia and systemic manifestations.	*Common* - diaper dermatitis. *Uncommon* - erythema, rash, petechiae.
Musculoskeletal and connective tissue disorders	*Rare* - muscle spasms, shaller pain. *Frequency unknown* - muscle weakness.	
Renal and urinary disorders	*Rare* - renal failure, acute renal failure.	
Pregnancy, puerperium and perinatal conditions	*Rare* – abortion.	
Reproductive system and breast disorders	*Rare* – bleeding from the genitals.	
General disorders and administration site conditions	*Uncommon* - hemorrhage, weakness/fatigue, fever, swelling/edema, chest pain. *Rare* - injection site lump, malaise.	*Common* - pain at the infusion site. *Uncommon* - burning at the infusion site, itching at the infusion site, erythema at the infusion site, erythema at the injection site, sensation of warmth at the infusion site.
Investigations		

	Adults aged 18 years and over	*Children and adolescents (from 3 months to 17 years)*
Biochemical blood test	*Common* - increased ALT, AST, alkaline phosphatase levels. *Uncommon* - increased levels of total, direct and indirect bilirubin, creatinine, urea and glucose in the blood serum. *Rare* - decreased levels of bicarbonate, creatinine and potassium in the blood serum; increased levels of lactate dehydrogenase, phosphates and potassium in the blood serum.	*Common* – increased ALT and AST levels.
General blood test	*Common* - increased platelet count. *Uncommon* - decreased white blood cell count, platelet count, segmented neutrophils, hemoglobin and hematocrit; increased eosinophil count, activated partial thromboplastin time, prothrombin time, segmented neutrophils and white blood cells. *Rare* - decreased lymphocyte count; increased number of bound neutrophils, lymphocytes, metamyelocytes, monocytes, myelocytes; atypical lymphocytes.	*Common* - decreased number of neutrophils. *Uncommon* - increased number of platelets, activated partial thromboplastin time, prothrombin time, decreased hemoglobin level.
Common urine test	*Uncommon* - increased content of bacteria, leukocytes, epithelial cells and erythrocytes in urine, presence of yeast fungi in urine. *Rare* - increased level of urobilinogen in urine.	
Other	*Uncommon*: positive test for *Clostridium difficile* toxins.	

Reporting suspected adverse reactions

It is important to report suspected reactions after registration of the medicinal product in order to ensure continuous monitoring of the benefit-risk ratio of the medicinal product. Healthcare professionals are encouraged to report any suspected adverse reactions of the medicinal product through the national adverse reaction reporting systems of the Eurasian Economic Union member states. In the Republic of Belarus, it is recommended to report adverse

reactions to the information database on adverse reactions (effects) to medicinal products, including reports of medicinal product inefficiency (Center for Examinations and Tests in Health Service Unitary Enterprise of the Ministry of Health of the Republic of Belarus, www.rceth.by)

4.9 Overdose

There is no specific information on the treatment of overdose with ertapenem. Overdose with ertapenem is unlikely. Intravenous administration of ertapenem at a dose of 3 g per day for 8 days to healthy adult volunteers did not lead to significant toxicity. In clinical studies in adult patients, 3 g of the medicinal product per day did not cause clinically significant adverse reactions. In clinical studies in children, a single intravenous dose of 40 mg/kg to a maximum of 2 g was not accompanied by toxic manifestations.

However, in case of overdose, treatment with Ertapenem-TF shall be discontinued and general maintenance treatment shall be administered until the medicinal product is eliminated by the kidneys.

Ertapenem is eliminated to a certain extent by hemodialysis (see section 5.2). However, there is no information on hemodialysis for the treatment of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group Antibacterial agents for systemic use. Carbapenems.

ATC code J01DH03.

5.1.1. Mechanism of action

Ertapenem inhibits cell wall synthesis by binding to penicillin-binding proteins (PBPs). *Escherichia coli* has a stronger affinity for PBPs 2 and 3.

Pharmacokinetic/pharmacodynamic (PK/PD) relationship

Similar to other beta-lactam antibiotics, preclinical PK/PD studies have demonstrated that the time in which ertapenem plasma concentrations exceed the minimum inhibitory concentration of the pathogen optimally correlates with efficacy.

Mechanism of resistance

In observational studies conducted in Europe, resistance was uncommon among species sensitive to ertapenem. Among resistant strains, some were resistant to other carbapenem antibacterial medicinal products. Ertapenem is virtually stable to hydrolysis by most classes of beta-lactamases, including penicillinases, cephalosporinases, and extended-spectrum beta-lactamases, but not by metallo-beta-lactamases.

Methicillin-resistant staphylococci and enterococci are resistant to ertapenem because of nonsusceptibility of the target PBP; *P. aeruginosa* and other nonfermentative bacteria are usually resistant, possibly because of limited penetration and active efflux.

Resistance is uncommon in enterobacteriaceae; Ertapenem is generally active against enterobacteriaceae with extended-spectrum beta-lactamases (ESBLs). However, resistance may occur when ESBLs or other potent beta-lactamases (e.g., AmpC types) are present concomitantly with impaired permeability resulting from the loss of one or more outer membrane porins or from activation of the efflux pump. Resistance may also arise from the assembly of beta-lactamases with potent carbapenem-hydrolyzing activity (e.g., IMP and VIM metallo-beta-lactamases or KPC types), although this is 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-dependent cross-resistance between ertapenem and these medicinal products. However, microorganisms may exhibit resistance to more than one class of antibacterial medicinal products when the mechanism is (or includes) the impermeability of certain substances and/or is mediated by an efflux pump.

Cutoff concentrations

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) has established the following minimum inhibitory concentration (MIC) values, S – susceptibility, R – resistance.
Enterobacterales: S ≤ 0.5 mg/L and R > 0.5 mg/L
Streptococcus pneumoniae: S ≤ 0.5 mg/L and R > 0.5 mg/L
Haemophilus influenzae: S ≤ 0.5 mg/L and R > 0.5 mg/L
M. catarrhalis: S ≤ 0.5 mg/L and R > 0.5 mg/L
Gram-negative anaerobes: S ≤ 0.5 mg/L and R > 0.5 mg/L
Gram-positive anaerobes: S ≤ 0.5 mg/L and R > 0.5 mg/L
Viridans group streptococci: S ≤ 0.5 mg/L and R > 0.5 mg/L
Non-species-specific breakpoints: S ≤ 0.5 mg/L and R > 0.5 mg/L
(Note: the susceptibility of staphylococci to ertapenem depends on susceptibility to methicillin, and the susceptibility of groups A, B, C, and G streptococci depends on susceptibility to benzylpenicillin.)
Physicians are aware that local MIC breakpoints, if available, shall be taken into account.
Microbiological susceptibility
Acquired resistance may vary geographically and over time for individual bacterial species, so local resistance data are desirable, especially when treating severe infections. If the efficacy of a medicinal product against at least some types of infections is in doubt, expert advice shall be sought.
The information below provides only approximate data on the possible susceptibility or non-susceptibility of microorganisms.
Usually sensitive microorganisms:
Gram-positive aerobes:
Methicillin-sensitive staphylococci (including *Staphylococcus aureus*)*
*Streptococcus agalactiae **
*Streptococcus pneumoniae **[a]
Streptococcus pyogenes
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:
Microorganisms of the genus *Clostridium* (excluding *C. difficile*) *
Microorganisms of the genus *Eubacterium **
Microorganisms of the genus *Fusobacterium **
Microorganisms of the genus *Peptostreptococcus **
*Porphyromonas asaccharolytica **
Microorganisms of the genus *Prevotella **
Microorganisms that can acquire resistance:
Gram-positive aerobes:
Methicillin-resistant staphylococci [bc]

Anaerobes:
Bacteroides fragilis and species of *B. fragilis* group *
Microorganisms with natural resistance:
Gram-positive aerobes:
Corynebacterium jeikeium
Enterococci, including *Enterococcus faecalis* and *Enterococcus faecium*
Gram-negative aerobes:
Microorganisms of the genus *Aeromonas*
Microorganisms of the genus *Acinetobacter*
Burkholderia cepacia
Pseudomonas aeruginosa
Stenotrophomonas maltophilia
Anaerobes:
Microorganisms of the genus *Lactobacillus*
Other:
Microorganisms of the genus *Chlamydia*
Microorganisms of the genus *Mycoplasma*
Microorganisms of the genus *Rickettsia*
Microorganisms of the genus *Legionella*

* Activity has been satisfactorily demonstrated in clinical studies.

[a] The efficacy of Ertapenem-TF in the treatment of community-acquired pneumonia caused by penicillin-resistant *Streptococcus pneumonia* has not been established.

[b] In some countries the incidence of acquired resistance is > 50%.

[c] Methicillin-resistant staphylococci (including MRSA) are always resistant to beta-lactams.

Information on clinical trials

Efficacy in pediatric trials

Ertapenem was evaluated primarily for paediatric safety and secondarily for efficacy in randomised, comparative, multicenter studies in patients aged 3 months to 17 years. The proportion of patients with favorable clinical responses at post-treatment visits in the clinically modified target (MITT) population is shown below:

Disease [#]	Age	Ertapenem		Ceftriaxone	
		n/m	%	n/m	%
Community-acquired pneumonia (CAP)	3 - 23 months	31/35	88.6	13/13	100.0
	2 - 12 years	55/57	96.5	16/17	94.1
	13 - 17 years	3/3	100.0	3/3	100.0
Disease	Age	Ertapenem		Ticarcillin/clavulanate	
		n/m	%	n/m	%
Intra-abdominal infections (IAI)	3 - 23 months	28/34	82.4	7/9	77.8
	2 - 12 years	15/16	93.8	4/6	66.7
Pelvic inflammatory disease (PID)	13 - 17 years	25/25	100.0	8/8	100.0

[#] Including 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 bacteremia at baseline.

5.2 Pharmacokinetic properties

Plasma concentrations

Mean plasma ertapenem concentrations following a single 30-minute intravenous infusion of 1000 mg to healthy adult volunteers (25 to 45 years) were 155 mcg/mL (C_{max}) in 0.5 hours

post-dose (end of infusion), 9 mcg/mL in 12 hours post-dose, and 1 mcg/mL in 24 hours post-dose. The area under the plasma concentration curve (AUC) of ertapenem in adults increases nearly proportionally to dose over the dose range of 0.5 to 2 g.
There is no accumulation of ertapenem in adults after multiple intravenous doses over the dose range of 0.5 to 2 g.
Mean plasma ertapenem concentrations after a single 30-minute intravenous infusion of 15 mg/kg (up to a maximum dose of 1000 mg) in patients aged 3 to 23 months were 103.8 mcg/mL (C_{max}) in 0.5 hours post-dose (end of infusion), 13.5 mcg/mL in 6 hours post-dose, and 2.5 mcg/mL in 12 hours post-dose.
Mean plasma ertapenem concentrations following a single 30-minute intravenous infusion of 15 mcg/kg (up to a maximum dose of 1000 mg) in patients aged 2 to 12 years were 113.2 mcg/mL (C_{max}) in 0.5 hours post-dose (end of infusion), 12.8 mcg/mL in 6 hours post-dose, and 3.0 mcg/mL in 12 hours post-dose. Mean plasma ertapenem concentrations following a single 30-minute intravenous infusion of 20 mg/kg (up to a maximum dose of 1000 mg) in patients aged 13 to 17 years were 170.4 mcg/mL (C_{max}) in 0.5 hours post-dose (end of infusion), 7.0 mcg/mL in 12 hours post-dose, and 1.1 mcg/mL in 24 hours post-dose. Mean plasma ertapenem concentrations following a single 30-minute intravenous infusion of 1000 mg in three patients aged 13 to 17 years were 155.9 mcg/mL (C_{max}) in 0.5 hours post-dose (end of infusion) and 6.2 mcg/mL in 12 hours post-dose.

Distribution

Ertapenem is easily bound to human plasma proteins. In healthy young adults (25 to 45 years of age), protein binding decreases with increasing plasma concentrations, from approximately 95% bound at an approximate plasma concentration of <50 mcg/mL to approximately 92% bound at an approximate plasma concentration of 155 mcg/mL (mean concentrations were achieved at the end of a 1000 mg intravenous infusion).
The volume of distribution (V_{dss}) of ertapenem in adults is approximately 8 L (0.11 L/kg), in children aged 3 months to 12 years it is approximately 0.2 L/kg, and in children aged 13 to 17 years it is approximately 0.16 L/kg.
Ertapenem concentrations achieved in blister fluid at each sampling time on day 3 of intravenous dosing at 1000 mg once daily demonstrated a blister fluid to plasma AUC ratio 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 insignificant. The change in binding was <12% at peak plasma ertapenem concentrations following a 1000 mg dose. *In vitro*, probenecid (500 mg every 6 hours) reduced the fraction of ertapenem bound in plasma at the end of infusion in humans receiving a single 1000 mg intravenous dose by approximately 91% to 87%. The effects of this change are expected to have short duration. It is unlikely that clinically significant interactions will occur due to ertapenem displacing other medicinal products or vice versa.
In vitro studies show that ertapenem does not inhibit P-glycoprotein-mediated transport of digoxin or vinblastine, and is not a substrate for either.

Metabolism

In healthy young adults (23 to 49 years) following intravenous infusion of 1000 mg radiolabeled ertapenem, the source of radioactivity in plasma was ertapenem (94%). The major metabolite of ertapenem is a 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 6 major CYP isoforms: 1A2, 2C9, 2D6, 2E1 and 3A4.

Elimination

Following intravenous administration of 1000 mg radiolabeled ertapenem to healthy young adults (23 to 49 years), approximately 80% of the medicinal product was recovered in the urine and 10% in the feces. Of the 80% recovered in the urine, approximately 38% was

excreted as unchanged ertapenem and approximately 37% was excreted as the ring-opened metabolite. In healthy young adults (18 to 49 years) and in patients 13 to 17 years of age, the mean plasma half-life of 1000 mg intravenously was 4 hours, and in children 3 months to 12 years of age, approximately 2.5 hours. Mean urinary ertapenem concentrations exceed 984 mcg/mL in 0-2 hours post-dose and exceed 52 mcg/mL in 12-24 hours post-dose.

Special populations

Sex

Plasma concentrations of ertapenem are comparable in men and women.

Elderly

Plasma concentrations following intravenous administration of 1000 and 2000 mg ertapenem are slightly higher (approximately 39% and 22%, respectively) in healthy elderly subjects (≥ 65 years) than in younger subjects (< 65 years). No dosage adjustment is necessary in elderly patients unless severe renal impairment is present.

Pediatric population

Plasma ertapenem concentrations are comparable in children aged 13 to 17 years and in adults following intravenous administration of 1000 mg daily.

After administration of 20 mg/kg (up to a maximum dose of 1000 mg), pharmacokinetic parameters in patients aged 13 to 17 years were generally comparable to those in healthy young adults. In order to evaluate pharmacokinetic data, if all patients in this age group had received the medicinal product at a dose of 1000 mg, pharmacokinetic data were calculated with adjustment for the 1000 mg dose, assuming linearity. Comparison of the results shows that when administered at a dose of 1000 mg once daily, ertapenem achieves a comparable pharmacokinetic profile in patients aged 13 to 17 years and in adults. The ratios (13-17 years/adults) for AUC, end-of-infusion, and mid-dose concentrations were 0.99, 1.20, and 0.84, respectively. Mid-dose plasma concentrations following a single intravenous dose of 15 mg/kg ertapenem in patients 3 months to 12 years of age are comparable to mid-dose plasma concentrations following a single intravenous dose of 1000 mg ertapenem in adults (see "Plasma concentrations"). Plasma clearance (mL/min/kg) of ertapenem is approximately 2-fold higher in patients 3 months to 12 years of age compared to adults. At a dose of 15 mg/kg, AUC and plasma concentrations at the midpoint of dosing in patients aged 3 months to 12 years were comparable to those in healthy young adults receiving 1000 mg intravenous ertapenem.

Hepatic impairment

The pharmacokinetics of ertapenem in patients with hepatic impairment have not been studied. Due to the limited metabolism of ertapenem in the liver, the pharmacokinetics of the medicinal product are not expected to be altered by hepatic impairment. Therefore, no dosage adjustment is necessary in patients with hepatic impairment.

Renal impairment

Following a single 1000 mg intravenous dose of ertapenem in adults, AUC values for total ertapenem (bound and unbound) and unbound ertapenem are similar in patients with mild renal impairment (creatinine clearance 60 to 90 mL/min/1.73 m^2) and in healthy subjects (25 to 82 years of age). AUC values for total ertapenem and unbound ertapenem are increased approximately 1.5-fold and 1.8-fold, respectively, in patients with moderate renal impairment (creatinine clearance 31 to 59 mL/min/1.73 m^2) compared with healthy subjects. The AUC values for total ertapenem and unbound ertapenem are increased approximately 2.6-fold and 3.4-fold, respectively, in patients with severe renal impairment (creatinine clearance 5 to 30 mL/min/1.73 m^2) compared with healthy subjects. The AUC values for total ertapenem and unbound ertapenem are increased approximately 2.9-fold and 6.0-fold, respectively, between dialysis sessions in patients undergoing hemodialysis compared with healthy subjects. Following a single 1000 mg intravenous dose immediately prior to hemodialysis, approximately 30% of the dose was recovered in the dialysate. There are no data in children with renal impairment. There are insufficient data on the safety and efficacy of ertapenem in

patients with end-stage renal impairment and in patients requiring hemodialysis to establish dosage recommendations. Therefore, ertapenem shall not be used in these populations.

5.3 Preclinical safety data
Preclinical data do not demonstrate a specific risk for humans based on accepted studies of safety, pharmacology, repeated dose toxicity, genotoxicity, and reproductive and developmental toxicity. However, a decrease in neutrophil counts was observed in rats administered high doses of ertapenem, which is not considered a significant safety concern. Long-term animal studies to evaluate the carcinogenic potential of ertapenem have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium bicarbonate, sodium hydroxide.

6.2 Incompatibilities
Solvents or infusion solutions containing dextrose shall not be used for reconstitution or administration of ertapenem.
As compatibility studies have not been performed, this medicinal product shall not be used concomitantly with other medicinal products except those listed in section 6.6.

6.3 Expiry date (Shelf life)
2 years
Do not use after the expiration date.
Unopened vials (before reconstitution)
Store in the original packaging (protect from light) at a temperature below 25°C.
Reconstituted solutions
The diluted solution shall be used immediately. From a microbiological point of view, the medicinal product shall be used immediately, otherwise the responsibility for the storage time and conditions during use lies with the consumer. Diluted solutions (approximately 20 mg/ml ertapenem) are physically and chemically stable for 6 hours at a temperature below 25°C or for 24 hours at a temperature of 2°C to 8°C (in the refrigerator). Solutions shall be used within 4 hours after removal from the refrigerator. Solutions of Ertapenem-TF shall not be frozen.

6.4 Special precautions for storage
Store in original packaging (protected from light) at a temperature below 25°C.
Do not use after the expiry date stated on the packaging.

6.5 Nature and contents of container
1000 mg of ertapenem in 20 ml vials of hydrolytic class I. The vials are sealed with rubber stoppers and rolled with aluminum caps with a plastic flip-off lid. 1 or 5 vials together with instructions for medical use in a cardboard pack.

6.6 Special precautions for disposal of used medicinal product or waste obtained after use of the medicinal product and other medicinal product handling
Adults and adolescents 13 to 17 years of age
Reconstitution
Reconstitute the contents of the vial (1000 mg of Ertapenem-TF) with 10 mL of water for injection or 0.9% (9 mg/mL) sodium chloride solution to obtain a reconstituted solution of approximately 100 mg/mL. Mix well until completely dissolved.
Dilution

For 50 mL sachets: For the 1000 mg dose, immediately transfer the contents of the reconstituted vial to a 50 mL bag containing 0.9% (9 mg/mL) sodium chloride solution; or
For 50 mL vials: For the 1000 mg dose, remove 10 mL from the 50 mL vial containing 0.9% (9 mg/mL) sodium chloride solution. Transfer the contents of the reconstituted vial to a 50 mL vial containing 0.9% (9 mg/mL) sodium chloride.
Infusion
Administer as an infusion over 30 minutes.
Children (3 months to 12 years)
Reconstitution
Reconstitute the contents of the vial (1000 mg of Ertapenem-TF) with 10 mL of water for injection or 0.9% (9 mg/mL) sodium chloride to obtain a reconstituted solution of approximately 100 mg/mL. Mix well until completely dissolved.
Dilution
For diluent in bags: transfer a volume of reconstituted solution equivalent to 15 mg/kg body weight (not to exceed 1000 mg/day) into a bag containing 0.9% (9 mg/mL) sodium chloride solution to obtain a final concentration of 20 mg/mL or less; or
For diluent in vials: transfer a volume of reconstituted solution equivalent to 15 mg/kg body weight (not to exceed 1000 mg/day) into a vial containing 0.9% (9 mg/mL) sodium chloride solution to obtain a final concentration of 20 mg/mL or less.
Infusion
Administer as an infusion over 30 minutes.
Reconstituted solution shall be diluted in 9 mg/mL (0.9%) sodium chloride solution immediately after preparation. From a microbiological point of view, the medicinal product shall be used immediately, otherwise the responsibility for the storage time and conditions during use lies with the consumer. Diluted solutions (approximately 20 mg/ml of ertapenem) are physically and chemically stable for 6 hours at a temperature not exceeding 25°C or for 24 hours at a temperature of 2°C to 8°C (in a refrigerator). Solutions shall be used within 4 hours after removal from the refrigerator. Solutions of the medicinal product Ertapenem-TF shall not be frozen.
Before administration, reconstituted solutions shall be checked for particulate matter and color change. Solutions of Ertapenem-TF are colorless to pale yellow. Color changes within this range do not affect the strength.
For the shelf life of the diluted solution, see section 6.3.
Any unused medicinal product or waste shall be disposed of in accordance with the established procedure.

6.7 Prescription status
On prescription.

7. MARKETING AUTHORISATION HOLDER
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8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorisation:
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT