PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

NIVAZEN 1 g powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains ertapenem sodium equivalent to 1,0 g ertapenem.

The reconstituted solution contains 100 mg/ml ertapenem.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

A sterile, pyrogen-free white to yellowish powder.

After reconstitution: A clear solution free from visible particles.

pH: 7,0 to 8,0.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

NIVAZEN is indicated for the treatment of adult patients with the following moderate to severe infections caused by susceptible strains of the designated micro-organisms (see section 4.2):

Complicated intra-abdominal infections due to *Escherichia coli, Clostridium clostridioforme, Eubacterium lentum, Peptostreptococcus species, Bacteroides fragilis, Bacteroides distasonis, Bacteroides ovatus, Bacteroides thetaiotaomicron* or *Bacteroides uniformis.*

Complicated skin and skin structure infections including diabetic lower extremity and diabetic foot infections due to *Staphylococcus aureus (*methicillin susceptible strains only*), Streptococcus agalactiae, Streptococcus pyogenes, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Porphyromonas asaccharolytica* or *Peptostreptococcus species.*

Community acquired pneumonia due to *Streptococcus pneumoniae* (penicillin susceptible strains only) including cases with concurrent bacteraemia, *Moraxella catarrhalis.* If Community Acquired Pneumonia is caused by *Haemophilus influenzae*, NIVAZEN should be used only following confirmation of culture and sensitivity results.

Complicated urinary tract infections including pyelonephritis due to *Escherichia coli,* including cases with concurrent bacteraemia or *Klebsiella pneumoniae.*

Acute pelvic infections including post-partum endomyometritis, septic abortion and post-surgical gynaecologic infections due to *Streptococcus agalactiae, Escherichia coli, Bacteroides fragilis, Porphyromonas asaccharolytica, Peptostreptococcus* species or *Prevotelia bivia.*

Paediatric use

Safety and effectiveness of NIVAZEN 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 with the following infections:

- Complicated intra-abdominal infections
- Complicated skin and skin structure infections
- Community acquired pneumonia
- Complicated urinary tract infections
- Acute pelvic infections.

Appropriate specimens for bacteriological examination should be obtained in order to isolate

and identify the causative organisms and to determine their susceptibility to ertapenem. Therapy with NIVAZEN (ertapenem) may be initiated empirically before results of these tests are known; once results become available, antimicrobial therapy should be adjusted accordingly.

4.2 Posology and method of administration

Posology

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

The usual duration of therapy with NIVAZEN is 3 to 14 days but varies by the type of infection and causative pathogen(s) (see section 4.1). When clinically indicated, a switch to an appropriate oral antimicrobial may be implemented if clinical improvement has been observed.

Dosage guidelines for adults and paediatric patients with normal renal function and body weight			
Infection	**Daily dose (IV or IM) adults and paediatric patients 13 years of age and older**	**Daily dose (IV or IM) paediatric patients 3 months to 12 years of age**	**Recommended duration of total antimicrobial treatment**
Complicated intra-abdominal infections	1 g	15 mg/kg twice daily[§]	5 to 14 days
Complicated skin and skin structure infections including diabetic lower	1 g	15 mg/kg twice daily[§]	7 to 14 days [#]

Dosage guidelines for adults and paediatric patients with normal renal function and body weight			
Infection	**Daily dose (IV or IM) adults and paediatric patients 13 years of age and older**	**Daily dose (IV or IM) paediatric patients 3 months to 12 years of age**	**Recommended duration of total antimicrobial treatment**
extremity and diabetic foot infections			
Community acquired pneumonia	1 g	15 mg/kg twice daily[§]	10 to 14 days[†]
Complicated urinarytract infections including pyelonephritis	1 g	15 mg/kg twice daily[§]	10 to 14 days[†]
Acute pelvic infections including postpartum endomyometritis, septic abortion and post-surgical gynaecologic Infections	1 g	15 mg/kg twice daily[§]	3 to 10 days

Dosage guidelines for adults and paediatric patients with normal renal function and body weight			
Infection	**Daily dose (IV or IM) adults and paediatric patients 13 years of age and older**	**Daily dose (IV or IM) paediatric patients 3 months to 12 years of age**	**Recommended duration of total antimicrobial treatment**
¨defined as creatinine clearance > 90 ml/min/1,73 m^2. †duration includes a possible switch to an appropriate oral therapy once clinical improvement has been demonstrated. §not to exceed 1 g/day. #patients with diabetic foot infections received up to 28 days of treatment (parenteral or parenteral plus oral switch therapy).			

Special populations

Renal impairment

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

Haemodialysis

Following a single 1 g IV dose of ertapenem given immediately prior to a haemodialysis session, approximately 30 % of the dose was recovered in the dialysate. When adult patients on haemodialysis are given 500 mg NIVAZEN within 6 hours prior to haemodialysis, a supplementary dose of 150 mg is recommended following the haemodialysis session. If

NIVAZEN is given as least 6 hours prior to haemodialysis, no supplementary dose is needed. There are no data on paediatric patients on haemodialysis, nor patients undergoing peritoneal dialysis or hemofiltration.

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

Males: (weight in kg) x (140 - age in years)

(72) x serum creatinine (mg/100 ml)

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

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

Hepatic impairment

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

Elderly

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

Method of administration

NIVAZEN may be administered by intravenous (IV) infusion or intramuscular (IM) injection. When administered intravenously, NIVAZEN should be infused over a period of 30 minutes. Intramuscular administration of NIVAZEN may be used as an alternative to intravenous administration in the treatment of those infections for which intramuscular therapy is appropriate.

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

4.3 Contraindications

- Hypersensitivity to ertapenem or to any of the excipients of NIVAZEN (see section 6.1).
- Hypersensitivity to any other carbapenem antibacterial medicine.
- Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial medicines (e.g. penicillins or cephalosporins).
- IM administration of NIVAZEN for patient who is hypersensitive to local anaesthetics of amide type and patients with severe shock or heart block. (Lidocaine hydrochloride is used as diluent for IM preparation, see section 6.6.)
- Infants under 3 months as no safety and efficacy data are available.
- Treatment of meningitis, as NIVAZEN does not penetrate cerebrospinal fluid (CSF) sufficiently.

4.4 Special warnings and precautions for use

Hypersensitivity

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH BETA-LACTAMS, INCLUDING NIVAZEN. 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 NIVAZEN, 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 NIVAZEN OCCURS (see section 4.8), DISCONTINUE THE THERAPY IMMEDIATELY. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE (ADRENALINE), OXYGEN,**

INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION. OTHER THERAPY MAY ALSO BE ADMINISTERED AS INDICATED.

Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8)

Superinfection

Prolonged use of ertapenem, as in NIVAZEN 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

Pseudomembranous colitis (antibiotic-associated colitis) has been reported with ertapenem, as in NIVAZEN 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 NIVAZEN.

Treatment with NIVAZEN alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis". After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to medicine discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, parenteral nutrition and treatment with an antibacterial medicine clinically effective against *Clostridium difficile* colitis.

Seizures

Seizures have been reported during clinical investigation in adult patients treated with NIVAZEN (see section 4.8) During clinical investigations in adult patients treated with ertapenem (1 g once a day), seizures, irrespective of medicine relationship, occurred in 0,5 % of patients during study therapy plus 14 days follow-up period. These experiences have occurred more frequently in patients with central nervous system (CNS) disorders (e.g. brain lesions or history of seizures) and/or compromised renal function. Close adherence to the

recommended dosage regimen is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorder. If focal tremors, myoclonus or seizures occur, patients should be evaluated neurologically and the dosage of NIVAZEN re-examined to determine whether it should be decreased or discontinued.

Concomitant use with valproic acid

Co-administration of carbapenems, including ertapenem, to patients receiving valproic acid or divalproex sodium results in a reduction in valproic acid concentrations. The valproic acid concentrations may drop below the therapeutic range as a result of this interaction, therefore increasing the risk of breakthrough seizures. Increasing the dose of valproic acid or divalproex sodium may not be sufficient to overcome this interaction. The concomitant use of ertapenem, as in NIVAZEN and valproic acid/divalproex sodium is not recommended. Antibacterials other than carbapenems should be considered to treat infections in patients whose seizures are well controlled on valproic acid or divalproex sodium. If administration of NIVAZEN is necessary, supplemental anti-convulsant therapy should be considered (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.

Intramuscular use

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

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, evaluable patients

treated with ertapenem had severe disease (defined as pneumonia severity index > III). In another clinical study for the treatment of acute gynaecologic infections, in adults, evaluable patients treated with ertapenem had severe disease (defined as temperature ≥ 39 °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, some had generalised peritonitis and others 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 ≥ 15 and efficacy in these patients has not been established.

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

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

There is relatively little experience with NIVAZEN 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 medicine contains approximately 6,0 mEq (approximately 137 mg) of sodium per 1,0 g dose which should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction

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

Valproic acid/sodium valproate

Decreases in valproic acid levels that may fall below the therapeutic range have been reported when valproic acid was co-administered with carbapenem medicines. 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

Safety in pregnancy has not been established.

Lactation

Ertapenem is excreted in human milk. Safety in lactation has not been established.

Fertility

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be informed that dizziness and somnolence have been reported with NIVAZEN (see section 4.8).

NIVAZEN may therefore influence patients' ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

Adult patients

The most frequent adverse reactions were diarrhoea, infused vein complication, nausea and headache.

The most frequently reported laboratory abnormalities were elevations in ALT, AST, alkaline phosphatase and platelet count.

Paediatric patients (3 months to 17 years of age)

The most frequent adverse reactions were diarrhoea, infusion site pain and infusion site erythema.

The most frequently reported laboratory abnormalities were decreases in neutrophil count, and elevations in ALT and AST.

b. Tabulated summary of adverse reactions

Adult patients

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Less frequent	Oral candidiasis, candidiasis, fungal infection, pseudomembranous enterocolitis, vaginitis, pneumonia, dermatomycosis, postoperative wound infection, urinary tract infection
Blood and lymphatic system disorders	Less frequent	Neutropenia, thrombocytopenia
Immune system disorders	Less frequent	Allergy
	Frequency unknown	Anaphylaxis including anaphylactoid reactions
Metabolism and nutrition disorders	Less frequent	Anorexia, hypoglycaemia
Psychiatric disorders	Less frequent	Insomnia, confusion, agitation, anxiety, depression
	Frequency	Altered mental status, (including aggression,

MedDRA system organ class	Frequency	Adverse reactions
	unknown	delirium, disorientation, mental status changes)
Nervous system disorders	Frequent	Headache
	Less frequent	Dizziness, somnolence, seizure (see section 4.4), taste perversion, tremor, syncope
	Frequency unknown	Hallucinations, depressed level of consciousness, dyskinesia, myoclonus, gait disturbance
Eye disorders	Less frequent	Scleral disorder
Cardiac disorders	Less frequent	Sinus bradycardia, arrhythmia, tachycardia
	Frequency unknown	Kounis syndrome
Vascular disorders	Frequent	Infused vein complication, phlebitis/thrombophlebitis
	Less frequent	Hypotension, haemorrhage, increased blood pressure
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea, pharyngeal discomfort, nasal congestion, cough, epistaxis, rales/rhonchi, wheezing
Gastrointestinal disorders	Frequent	Diarrhoea, nausea, vomiting
	Less frequent	Constipation, acid regurgitation, dry mouth, dyspepsia, abdominal pain, dysphagia, faecal incontinence, pelvic peritonitis, *C.difficile*-associated diarrhoea

MedDRA system organ class	Frequency	Adverse reactions
	Frequency unknown	Teeth staining
Hepato-biliary disorders	Less frequent	Cholecystitis, jaundice, liver disorder
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus
	Less frequent	Erythema, urticaria, dermatitis, desquamation, hypersensitivity vasculitis
	Frequency unknown	Acute Generalised Exanthematous Pustulosis (AGEP), Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome), linear IgA disease.
Musculoskeletal and connective tissue disorders	Less frequent	Muscle cramp, shoulder pain
	Frequency unknown	Muscular weakness
Renal and urinary disorders	Less frequent	Renal insufficiency, acute renal insufficiency
Pregnancy, puerperium, and perinatal conditions	Less frequent	Abortion
Reproductive system and breast disorders	Less frequent	Vaginal pruritus, genital bleeding
General disorders and administration site conditions	Less frequent	Extravasation, asthenia/fatigue, fever, oedema/swelling, chest pain, pain, injection-site induration, malaise
Investigations		
Chemistry	Frequent	Elevations in ALT, AST,

MedDRA system organ class	Frequency	Adverse reactions
		alkaline phosphatase
	Less frequent	Increase in total serum bilirubin, direct serum bilirubin, indirect serum bilirubin, serum creatinine, serum urea, serum glucose, serum creatinine, decreases in serum bicarbonate, decrease in serum potassium, increases in serum LDH, serum phosphorus, serum potassium
Haematology	Frequent	Elevation in platelet count
	Less frequent	Decreases in white blood cells, platelet count, segmented neutrophils, haemoglobin, and haematocrit; increases in eosinophils, prothrombin time, monocytes, activated partial thromboplastin time, segmented neutrophils and white blood cells, decrease in lymphocytes, increases in band neutrophils, lymphocytes, metamyelocytes, myelocytes; atypical lymphocytes
Urinalysis	Less frequent	Increases in urine bacteria, urine epithelial cells and urine red blood cells, urine white blood cells, urine yeast present, increase in urobilinogen
Miscellaneous	Less frequent	Positive *Clostridium difficile* toxin

Paediatric patients (3 months to 17 years of age)

MedDRA system organ class	**Frequency**	**Adverse reactions**
Psychiatric disorders	Frequency unknown	Altered mental status (including aggression)
Nervous system disorders	Less frequent	Headache
	Frequency unknown	Hallucinations
Vascular disorders	Less frequent	Hot flush, hypertension
Gastrointestinal disorders	Frequent	Diarrhoea, vomiting
	Less frequent	Faeces discoloured, melena
Skin and subcutaneous tissue disorders	Frequent	Diaper dermatitis
	Less frequent	Rash, petechiae, erythema
General disorders and administration site conditions	Frequent	Infusion site pain
	Less frequent	Infusion site phlebitis, infusion site swelling, infusion site pruritus, infusion site warmth, infusion site burning, infusion site erythema
Investigations		
Chemistry	Frequent	Elevations in ALT and AST
Haematology	Frequent	Decreases in neutrophil count
	Less frequent	Decreases in white blood cells and increase in eosinophils, increases in platelet count, activated partial thromboplastin time, prothrombin time, decreases in haemoglobin

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4. 9 Overdose

No specific information is available on the treatment of overdosage with NIVAZEN. In the event of overdose, NIVAZEN should be discontinued, and general supportive care treatment given until renal elimination takes place. NIVAZEN can be removed by haemodialysis; however, no information is available on the use of haemodialysis to treat overdosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.20.1.1 Broad and medium spectrum antibiotics

Pharmacotherapeutic group: Antibacterials for systemic use, carbapenems

ATC code: J01DH03

Ertapenem is a synthetic, long-acting 1-β methyl-carbapenem that is structurally related to beta-lactam antibiotics, such as penicillins and cephalosporins. The bactericidal activity of ertapenem results from the inhibition of cell wall synthesis and is mediated through ertapenem binding to penicillin binding proteins (PBPs). In *Escherichia coli*, it has strong affinity toward PBPs 1a, 1b, 2, 3, 4 and 5 with preference for PBPs 2 and 3.

Microbiology

Ertapenem has *in vitro* activity against a wide range of gram-positive and gram-negative aerobic and anaerobic bacteria. Ertapenem has significant stability to hydrolysis by most

classes of beta-lactamases, including penicillinases and cephalosporinases and extended spectrum beta-lactamases, but not metallo-beta-lactamases.

Resistant organisms

Corynebacterium spp, *Enterococcus* spp (including *Enterococcus faecalis* and *Enterococcus faecium*), methicillin resistant *Staphylococcus aureus*, methicillin resistant coagulase negative *Staphylococcus*, *Acinetobacter* spp, *Pseudomonas* spp, *Stenotrophomonas maltophilia*.

5.2 Pharmacokinetic properties

Absorption

Ertapenem reconstituted with 1 % lidocaine hydrochloride injection, (in saline without epinephrine (adrenaline)) is well absorbed. Following IM administration of ertapenem at the recommended dose of 1 g, the mean bioavailability is approximately 92 % and the mean peak plasma concentrations (C_{max}) are reached in approximately 2 hours (T_{max}).

Distribution

Ertapenem is highly bound to human plasma proteins. In healthy young adults, the protein binding of ertapenem decreases as plasma concentrations increase, from approximately 95 % bound at an approximate plasma concentration of < 100 micrograms (µg)/ml to approximately 85 % bound at an approximate plasma concentration of 300 µg/ml.

Average plasma concentrations (µg/ml) of ertapenem following a single 30 minute IV of a 1 g or 2 g dose or IM administration of a single 1 g dose in healthy young adults are presented in **Table 1.**

Table 1

Plasma concentrations of ertapenem in adults after single dose administration

Dose/ Route	Average plasma concentrations (µg/ml)								
	0,5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	18 hr	24 hr
1 g IV*	155	11	83	48	31	20	9	3	1
1 g IM	33	53	67	57	40	27	13	4	2
2 g IV*	283	202	145	86	58	36	16	5	2

*IV doses were infused at a constant rate over 30 minutes

Area under the plasma concentration curve (AUC) of ertapenem in adults increases nearly dose-proportionally over the 0,5 to 2 g dose range.

There is no accumulation of ertapenem in adults following multiple IV doses ranging from 0,5 to 2 g daily or IM doses of 1 g daily.

Average plasma concentration of ertapenem in paediatric patients is 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	18 hr	24 hr
3-23 months									
(15 mg/kg)**	103,8	57,3	43,6	23,7	13,5	8,2	2,5	-	103,8
(20 mg/kg)**	126,8	87,6	58,7	28,4	-	12,0	3,4	0,4	126,8
(40 mg/kg)^	199,1	144,1	95,7	58,0	-	20,2	7,7	0,6	199,1

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	18 hr	24 hr
2-12 years									
(15 mg/kg)**	113,2	63,9	42,1	21,9	12,8	7,6	3,0	-	113,2
(20 mg/kg)**	147,6	97,6	63,2	34,5	-	12,3	4,9	0,5	147,6
(40 mg/kg)^	241,7	152,7	96,3	55,6	-	18,8	7,2	0,6	241,7
13-17 years									
(20 mg/kg)**	170,4	98,3	67,8	40,4	-	16,0	7,0	1,1	170,4
(1 g)^^	155,9	110,9	74,8	-	24,0	-	6,2	-	155,9
(40 mg/kg)^	255,0	188,7	127,9	76,2	-	31,0	15,3	2,1	255,0

*IV doses were infused at a constant rate over 30 minutes

** Up to a maximum dose of 1 g/day

^ Up to a maximum dose of 2 g/day

^^ based on three patients receiving 1 g ertapenem who volunteered for pharmacokinetic assessment in one of the two safety and efficacy studies

The apparent volume of distribution (V_{dss}) of ertapenem in adults is approximately 8 litres (0,11 litre/kg) and approximately 0,2 litre/kg in paediatric patients 3 months to 12 years of age and approximately 0,16 litre/kg in paediatric patients 13 to 17 years of age.

Ertapenem penetrates 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 intravenous doses showed a ratio of AUC in skin blister fluid: AUC in plasma of 0,61.

Ertapenem penetrates into breast milk.

In vitro studies indicate that ertapenem does not inhibit P-glycoprotein-mediated transport of

digoxin or vinblastine and that ertapenem is not a substrate for P-glycoprotein-mediated transport (see section 4.5).

Metabolism

In healthy young adults, 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 hydrolysis of the beta-lactam ring. Ertapenem does not inhibit metabolism mediated by any of the six major CYP isoforms: 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4.

Elimination

Ertapenem is eliminated primarily by the kidneys. The mean plasma half-life in healthy young adults and patients 13 to 17 years of age is approximately 4 hours and approximately 2,5 hours in paediatric patients 3 months to 12 years of age.

Following administration of a 1 g radiolabelled intravenous 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 ertapenem and approximately 37 % as the ring-opened metabolite. In healthy young adults given a 1 g intravenous dose, 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

Elderly

Plasma concentrations following a 1 g and 2 g IV dose of ertapenem are slightly higher (approximately 39 % and 22 %, respectively) in elderly adults (≥ 65 years) relative to young adults (< 65 years). No dosage adjustment is necessary in elderly patients.

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.

Renal impairment

Following a single 1 g intravenous dose of ertapenem in adults, AUC is similar in patients with mild renal impairment (Cl_{cr} 60 to 90 ml/min/1,73 m^2) compared with healthy subjects (ages 25 to 82 years). AUC is increased in patients with moderate renal impairment (Cl_{cr} 31 to 59 ml/min/1,73 m^2) approximately 1,5-fold compared with healthy subjects. AUC is increased in patients with severe renal impairment (Cl_{cr} 5 to 30 ml/min/1,73 m^2) 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 m^2) approximately 2,9-fold compared with healthy subjects. Following a single 1 g IV dose given immediately prior to a haemodialysis session, approximately 30 % of the dose is recovered in the dialysate. There are no data in paediatric patients with renal insufficiency.

A dosage adjustment is recommended for patients with advanced or end-stage renal insufficiency (see section 4.2).

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 IV dose.

Following the 20 mg/kg dose (up to a maximum dose of 1 g), the pharmacokinetic parameter values in patients 13 to 17 years of age were generally comparable to those in healthy young adults. To provide an estimate of the pharmacokinetic data if all patients in this age group were to receive a 1 g dose, the pharmacokinetic data were calculated adjusting for a 1 g dose, assuming linearity. A comparison of results showed that a 1 g once daily dose of ertapenem

achieves a pharmacokinetic profile in patients 13 to 17 years of age comparable to that of adults. The ratios (13 to 17 years/Adults) for AUC, the end of infusion concentration and the concentration at the midpoint of the dosing interval were 0,99; 1,20 and 0,84 respectively.

Plasma concentrations at the midpoint of the dosing interval following a single 15 mg/kg IV dose of ertapenem in patients 3 months to 12 years of age are comparable to plasma concentrations at the midpoint of the dosing interval following a 1 g once daily intravenous 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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydrogen carbonate (E500)

Sodium hydroxide (E524) (pH adjustment)

6.2 Incompatibilities

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

In the absence of compatibility studies, NIVAZEN must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

2 years

Diluted solutions should be used immediately.

After reconstitution for IV administration: Diluted solutions (approximately 20 mg/ml ertapenem) are physically and chemically stable for 6 hours at room temperature (25 °C) or

for 24 hours at 2 to 8 °C (in a refrigerator). Solutions should be used within 4 hours of their removal from the refrigerator.

After reconstitution for intramuscular (IM) administration: the reconstituted solution should be used within 1 hour after preparation.

6.4 Special precautions for storage

Unopened vials: store at or below 25 °C.

For storage conditions after reconstitution of NIVAZEN 1 g, see section 6.3.

6.5 Nature and contents of container

20 ml glass vial with rubber stopper and flip-off seal.

Pack size: 10 vials are packed in an outer cardboard carton.

6.6 Special precautions for disposal and other handling

INSTRUCTIONS FOR USE

Patients 13 years of age and older

Preparation for intravenous administration:

DO NOT MIX OR CO-INFUSE NIVAZEN WITH OTHER MEDICATIONS.

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

NIVAZEN MUST BE RECONSTITUTED AND THEN DILUTED PRIOR TO ADMINISTRATION.

1. Reconstitute the contents of a 1 g vial of NIVAZEN with 10 ml of one of the following: Water for Injection, 0,9 % Sodium Chloride Injection (154 mmol/l) or Bacteriostatic Water for Injection.
2. Shake well to dissolve and immediately transfer contents of the reconstituted vial to 50 ml of 0,9 % Sodium Chloride Injection (154 mmol/l).
3. Complete the infusion within 6 hours of reconstitution.

Preparation for intramuscular administration:

NIVAZEN MUST BE RECONSTITUTED PRIOR TO ADMINISTRATION.

1. Reconstitute the contents of a 1 g vial of NIVAZEN with 3,2 ml of 1,0 % or maximum 3,2 ml of 2 % lidocaine hydrochloride injection*** (**without epinephrine**). Shake vial thoroughly to form solution. This represents the maximum recommended dose of lidocaine.
2. Immediately withdraw the contents of the vial and administer by deep intramuscular injection into a large muscle mass (such as the gluteal muscles or lateral part of the thigh).
3. The reconstituted IM solution should be used within 1 hour after preparation. **Note: The reconstituted solution should not be administered intravenously**.

***Refer to the prescribing information for lidocaine hydrochloride.

Paediatric patients 3 months to 12 years of age

Preparation for intravenous administration:

DO NOT MIX OR CO-INFUSE NIVAZEN WITH OTHER MEDICATIONS.

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

NIVAZEN MUST BE RECONSTITUTED AND THEN DILUTED PRIOR TO ADMINISTRATION.

1. Reconstitute the contents of a 1 g vial of NIVAZEN with 10 ml of one of the following: Water for Injection, 0,9 % Sodium Chloride Injection (154 mmol/l) or Bacteriostatic Water for Injection.
2. Shake well to dissolve and immediately withdraw a volume equal to 15 mg/kg of bodyweight (not to exceed 1 g/day) and dilute in 0,9 % Sodium Chloride Injection (154 mmol/l) to a final concentration of 20 mg/ml or less.
3. Complete the infusion within 6 hours of reconstitution.

Preparation for intramuscular administration:

NIVAZEN MUST BE RECONSTITUTED PRIOR TO ADMINISTRATION.

1. Reconstitute the contents of a 1 g vial of NIVAZEN with 3,2 ml of 1,0 % or maximum 3,2 ml

of 2,0 % lidocaine hydrochloride injection*** (**without epinephrine**). Shake vial thoroughly to form solution. This represents the maximum recommended dose of lidocaine.

2. Immediately withdraw a volume equal to 15 mg/kg of body weight (not to exceed 1g/day) and administer by deep intramuscular injection into a large muscle mass (such as the gluteal muscles or lateral part of the thigh).
3. The reconstituted IM solution should be used within 1 hour after preparation. **Note: The reconstituted solution should not be administered intravenously.**

***Refer to the prescribing information for lidocaine hydrochloride.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER

530143

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 July 2022

10 DATE OF REVISION OF THE TEXT

19 November 2024