SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

Implatinze 500mg/500mg powder in vial for solution for IV infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains of Implatinze 500mg/500mg powder in vial for solution for IV contains Imipenem monohydrate (Equivalent to Imipenem 500 mg) 530.08 mg and Cilastatin Sodium (Equivalent to Cilastatin 500 mg) 530.58 mg. Both Imipenem monohydrate / Cilastatin Sodium Mixed with Sodium bicarbonate 20mg.

3. PHARMACEUTICAL FORM

Vial for solution for IV infusion

Before reconstitution : White to Pale yellow powder
After reconstitution: Clear colorless to yellow solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Imipenem / Cilastatin are indicated for the treatment of the following infections in adults and children 1 year of age and above.

- complicated intra-abdominal infections
- Severe pneumonia including hospital and ventilator-associated pneumonia
- Intra- and post-partum infections
- Complicated urinary tract infections
- complicated skin and soft-tissue infections

It may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.
Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

The dose recommendations for Implatinze represent the quantity of imipenem/cilastatin to be administered.
The daily dose of Implatinze should be based on the type of infection and given in equally divided doses based on consideration of degree of susceptibility of the pathogen(s) and the patient's renal function.

1.4.1 Summary of Product Characteristics

Adults and adolescents

For patients with normal renal function (creatinine clearance of ≥90 ml/min), the recommended dose regimens are:

500 mg/500 mg every 6 hours OR

1000 mg/1000 mg every 8 hours OR every 6 hours

It is recommended that infections suspected or proven to be due to less susceptible bacterial species (such as *Pseudomonas aeruginosa*) and very severe infections (e.g. in neutropenic patients with a fever) should be treated with 1000 mg/1000 mg administered every 6 hours.

A reduction in dose is necessary when creatinine clearance is < 90 ml/min (see Table 3.2.P.2-3).

The maximum total daily dose should not exceed 4000 mg/4000 mg per day.

Renal impairment

To determine the reduced dose for adults with impaired renal function:

1. The total daily dose (i.e. 2000/2000, 3000/3000 or 4000/4000 mg) that would usually be applicable to patients with normal renal function should be selected.

2. From table 3.2.P.2-3 the appropriate reduced dose regimen is selected according to the patient's creatinine clearance. For infusion times see: Method of administration.

Table 3.2.P.2-3:

Creatinine clearance (mL/min) is:	**If TOTAL DAILT DOSE is: 2000 mg/day**	**If TOTAL DAILY DOSE is: 3000 mg/day**	**If TOTAL DAILY DOSE is: 4000 mg/day**
≥90 (normal)	500 q6h	1000 q8h	1000 q6h
Reduced dosage (mg) for patients with renal impairment:			
≥60	400 q6h	500 q6h	750 q8h
≥30	300 q6h	500 q8h	500 q6h
≥15	200 q6h	500 q12h	500 q12h

Patients with a creatinine clearance of <15 ml/min

These patients should not receive Implatinze unless haemodialysis is instituted within 48 hours.

Patients on haemodialysis

When treating patients with creatinine clearances of <15 ml/min who are undergoing dialysis use the dose recommendation for patients with creatinine clearances of 15 to 29 ml/min (see table 3.2.P.2-3)

Both imipenem and cilastatin are cleared from the circulation during haemodialysis. The patient should receive Implatinze after haemodialysis and at 12 hour intervals timed from the end of that haemodialysis session. Dialysis patients, especially those with background central nervous system (CNS) disease, should be carefully monitored; for patients on haemodialysis, Implatinze is recommended only when the benefit outweighs the potential risk of seizures.

Currently there are inadequate data to recommend use of Implatinze for patients on peritoneal dialysis.

Hepatic impairment

No dose adjustment is recommended in patients with impaired hepatic function.

Elderly population

No dose adjustment is required for the elderly patients with normal renal function.

Paediatric population ≥1 year of age

For paediatric patients ≥1 year of age, the recommended dose is 15/15 or 25/25 mg/kg/dose administered every 6 hours.

It is recommended that infections suspected or proven to be due to less susceptible bacterial species (such as *Pseudomonas aeruginosa*) and very severe infections (e.g. in neutropenic patients with a fever) should be treated with 25/25 mg/kg administered every 6 hours.

Paediatric population <1 year of age

Clinical data are insufficient to recommend dosing for children less than 1 year of age.

Paediatric population with renal impairment

Clinical data are insufficient to recommend dosing for paediatric patients with renal impairment (serum creatinine > 2 mg/dl).

Method of administration

Implatinze is to be reconstituted and further diluted prior to administration. Each dose of ≤500 mg/500 mg should be given by intravenous infusion over 20 to 30 minutes. Each dose >500 mg/500 mg should be infused over 40 to 60 minutes. In patients who develop nausea during the infusion, the rate of infusion may be slowed.

4.3 Contraindications

• Hypersensitivity to the active substances or to any of the excipients listed in section 6.1

• Hypersensitivity to any other carbapenem antibacterial agent

• Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterialagent (e.g. penicillins or cephalosporins).

4.4 Special warnings and precautions for use

General

The selection of imipenem/cilastatin to treat an individual patient should take into account the appropriateness of using acarbapenem antibacterial agent based on factors such as severity of the infection, the prevalence of resistance to othersuitable antibacterial agents and the risk of selecting for carbapenem-resistant bacteria.

Hypersensitivity

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapywith beta-lactams. These reactions are more likely to occur in individuals with a

history of sensitivity to multiple allergens.Before initiating therapy with Implatinze, careful inquiry should be made concerning previous hypersensitivity reactionsto carbapenems,

penicillins, cephalosporins, other beta-lactams and other allergens (see section 4.3). If an allergicreaction to Implatinze occurs, discontinue the therapy immediately.

Serious anaphylactic reactions requireimmediate emergency treatment.

Hepatic

Hepatic function should be closely monitored during treatment with imipenem/cilastatin due to the risk of hepatic toxicity(such as increase in transaminases, hepatic failure and fulminant hepatitis).

Use in patients with liver disease: patients with pre-existing liver disorders should have liver function monitored duringtreatment with imipenem/cilastatin. There is no dose adjustment necessary (see section 4.2).

Haematology

A positive direct or indirect Coombs test may develop during treatment with imipenem/cilastatin.

Antibacterial spectrum

The antibacterial spectrum of imipenem/cilastatin should be taken into account especially in life-threatening conditionsbefore embarking on any empiric treatment. Furthermore, due to the limited susceptibility of specific pathogensassociated with e.g. bacterial skin and soft-tissue infections, to imipenem/cilastatin, caution should be exercised. Theuse of imipenem/cilastatin is not suitable for treatment of these types of infections unless the pathogen is alreadydocumented and known to be susceptible or there is a very high suspicion that the most likely pathogen(s) would besuitable for treatment. Concomitant use of an appropriate anti-MRSA agent may be indicated when MRSA infections aresuspected or proven to be involved in the approved indications. Concomitant use of an aminoglycoside may be indicated when Pseudomonas aeruginosa infections are suspected or proven to be involved in the approved indications (seesection 4.1).

Interaction with valproic acid

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

Clostridioides difficile

Antibiotic-associated colitis and pseudomembranous colitis have been reported with imipenem/cilastatin and with nearlyall other anti-bacterial agents and may range from mild to life-threatening in severity. It is important to consider thisdiagnosis in patients who develop diarrhoea

during or after the use of imipenem/cilastatin (see section 4.8).Discontinuation of therapy with imipenem/cilastatin and the administration of specific treatment for Clostridioides difficile should be considered. Medicinal products that inhibit peristalsis should not be given.

Meningitis

Implatinze is not recommended for the therapy of meningitis.

Renal impairment

Imipenem-cilastatin accumulates in patients with reduced kidney function. CNS adverse reactions may occur if the doseis not adjusted to the renal function, see sections 4.2 and 4.4 “Central nervous system” in this section.

Central nervous system

CNS adverse reactions such as myoclonic activity, confusional states, or seizures have been reported, especially when recommended doses based on renal function and body weight were exceeded. These experiences have been reported most commonly in patients with CNS disorders (e.g. brain lesions or history of seizures) and/or compromised renal function in whom accumulation of the administered entities could occur. Hence close adherence to recommended dose schedules is urged especially in these patients (see section 4.2). Anticonvulsant therapy should be continued in patients with a known seizure disorder.

Special awareness should be made to neurological symptoms or convulsions in children with known risk factors for seizures, or on concomitant treatment with medicinal products lowering the seizures threshold.

If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically and placed on anticonvulsant therapy if not already instituted. If CNS symptoms continue, the dose of Implatinze should be decreased or discontinued.

Patients with creatinine clearances of <15 ml/min should not receive Implatinze unless hemodialysis is instituted within48 hours. For patients on hemodialysis, Implatinze is recommended only when the benefit outweighs the potential risk of seizures (see section 4.2).

Paediatric population

Clinical data are insufficient to recommend the use of Implatinze in children under 1 year of age or pediatric patients with impaired renal function (serum creatinine >2 mg/dl). See also above under

Central nervous system.

Sodium

1.4.1 Summary of Product Characteristics

This medicinal product contains 37.6 mg sodium (1.6 mmol) per vial, equivalent to 1.9% of the WHO recommended maximum daily intake of 2 g sodium for an adult. This should be taken into consideration by patients on a controlled sodium diet

4.5 Interaction with other medicinal products and other forms of interaction

Generalized seizures have been reported in patients who received ganciclovir and Implatinze. These medicinal productsshould not be used concomitantly unless the potential benefit outweighs the risks. Decreases in valproic acid levels that may fall below the therapeutic range have been reported when valproic acid wasco-administered with carbapenem agents. The lowered valproic acid levels can lead to inadequate seizure control;therefore, concomitant use of imipenem and valproic acid/sodium valproate is not recommended and alternativeantibacterial or anti-convulsant therapies should be considered (see section 4.4).
Oral anti-coagulants
Simultaneous administration of antibiotics with warfarin may augment its anti-coagulant effects. There have been many reports of increases in the anti-coagulant effects of orally administered anti-coagulant agents,including warfarin in patients who are concomitantly receiving antibacterial agents. The risk may vary with the underlyinginfection, age and general status of the patient so that the contribution of the antibiotic to the increase in INR(international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequentlyduring and shortly after co-administration of antibiotics with an oral anti-coagulant agent.
Concomitant administration of Implatinze and probenecid resulted in minimal increases in the plasma levels and plasmahalf-life of imipenem. The urinary recovery of active (non-metabolised) imipenem decreased to approximately 60% of thedose when Implatinze was administered with probenecid. Concomitant administration of Implatinze and probeneciddoubled the plasma level and half-life of cilastatin, but had no effect on urine recovery of cilastatin.
Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies for the use of imipenem/cilastatin in pregnant women.

Studies in pregnant monkeys have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Implatinze should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

Imipenem and cilastatin are excreted into the mother's milk in small quantities. Little absorption of either compound occurs following oral administration. Therefore, it is unlikely that the suckling

infant will be exposed to significant quantities. If the use of Implatinze is deemed necessary, the benefit of breast feeding for the child should be weighed against the possible risk for the child.

Fertility

There are no data available regarding potential effects of imipenem/cilastatin treatment on male or female 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, there are some sideeffects (such as hallucination, dizziness, somnolence, and vertigo) associated with this product that may affect somepatients' ability to drive or operate machinery (see section 4.8).

4.8 Undesirable effects

In clinical trials including 1,723 patients treated with imipenem/cilastatin intravenous the most frequently reportedsystemic adverse reactions that were reported at least possibly related to therapy were nausea (2.0%), diarrhoea (1.8%),vomiting (1.5%), rash (0.9%), fever (0.5%), hypotension (0.4%), seizures (0.4%) (see section 4.4), dizziness (0.3%),pruritus (0.3%), urticaria (0.2%), somnolence (0.2%). Similarly, the most frequently reported local adverse reactions werephlebitis/thrombophlebitis (3.1%), pain at the injection site (0.7%), erythema at the injection site (0.4%) and veininduration (0.2%). Increases in serum transaminases and in alkaline phosphatase are also commonly reported.

The following adverse reactions have been reported in clinical studies or during post-marketing experience.

All adverse reactions are listed under system organ class and frequency: Very common (≥1/10), Common (≥1/100 to<1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000) and not known (cannot beestimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

1.4.1 Summary of Product Characteristics

System Organ Class	Frequency	Event
Infections and infestations	Rare	pseudomembranous colitis, candidiasis
	Very rare	gastro-enteritis
Blood and lymphatic system disorders	Common	eosinophilia
	Uncommon	pancytopenia, neutropenia, leucopenia, thrombocytopenia, thrombocytosis
	Rare	agranulocytosis
	Very rare	haemolytic anaemia, bone marrow depression
Immune system disorders	Rare	anaphylactic reactions
Psychiatric disorders	Uncommon	psychic disturbances including hallucinations and confusional states
Nervous system disorders	Uncommon	seizures, myoclonic activity, dizziness, somnolence
	Rare	encephalopathy, paraesthesia, focal tremor, taste perversion
	Very rare	aggravation of myasthenia gravis, headache
	Not known	agitation, dyskinesia

1.4.1 Summary of Product Characteristics

Ear and labyrinth disorders	Rare	hearing loss
	Very rare	vertigo, tinnitus
Cardiac disorders	Very rare	cyanosis, tachycardia, palpitations
Vascular disorders	Common	thrombophlebitis
	Uncommon	hypotension
	Very rare	flushing
Respiratory, thoracic and mediastinal disorders	Very rare	dyspnoea, hyperventilation, pharyngeal pain
Gastrointestinal disorders	Common	diarrhoea, vomiting, nausea Medicinal product-related nausea and/or vomiting appear to occur more frequently in granulocytopenic patients than in non-granulocytopenic patients treated with PRIMAXIN
	Rare	staining of teeth and/or tongue
	Very rare	haemorrhagic colitis, abdominal pain, heartburn, glossitis, tongue papilla hypertrophy, increased salivation
Hepatobiliary disorders	Rare	hepatic failure, hepatitis
	Very rare	fulminant hepatitis
Skin and subcutaneous tissue disorders	Common	rash (e.g. exanthematous)
	Uncommon	urticaria, pruritus
	Rare	toxic epidermal necrolysis, angioedema, Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis
	Very rare	hyperhidrosis, skin texture changes
Musculoskeletal and connective tissue disorders	Very rare	polyarthralgia, thoracic spine pain
Renal and urinary disorders	Rare	acute renal failure, oligurial/anuria, polyuria, urine discoloration (harmless and should not be confused with haematuria) The role of PRIMAXIN in changes in renal function is difficult to assess, since factors predisposing to pre-renal azotemia or to impaired renal function usually have been present.
Reproductive system and breast disorders	Very rare	pruritus vulvae
General disorders and administration site conditions	Uncommon	fever, local pain and induration at the injection site, erythema at the injection site
	Very rare	chest discomfort, asthenia/weakness
Investigations	Common	increases in serum transaminases, increases in serum alkaline phosphatase
	Uncommon	A positive direct Coombs' test, prolonged prothrombin time, decreased haemoglobin, increases in serum bilirubin, elevations in serum creatinine, elevations in blood urea nitrogen

Paediatric population (≥3 months of age)

Pediatric population (≥3 months of age*)*

In studies of 178 pediatric patients ≥3 months of age, the reported adverse reactions were consistent with those reported for adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at:

www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of overdose that can occur are consistent with the adverse reaction profile; these may include seizures,confusion, tremors, nausea, vomiting, hypotension, bradycardia. No specific information is available on treatment ofoverdose with Implatinze. Imipenem-cilastatin sodium is haemodialyzable. However, usefulness of this procedure in theoverdose setting is unknown

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, carbapenems, ATC code: J01D H51
Mechanism of action
Implatinze consists of two components: imipenem and cilastatin sodium in a 1:1 ratio by weight. Imipenem, also referred to as N-formimidoyl-thienamycin, is a semi-synthetic derivative of thienamycin, the parentcompound produced by the filamentous bacterium
Streptomyces cattleya
.
Imipenem exerts its bactericidal activity by inhibiting bacterial cell wall synthesis in Gram-positive and Gram-negativebacteria through binding to penicillin-binding proteins (PBPs).
Cilastatin sodium is a competitive, reversible and specific inhibitor of dehydropeptidase-I, the renal enzyme whichmetabolizes and inactivates imipenem. It is devoid of intrinsic antibacterial activity and does not affect the antibacterialactivity of imipenem.
Pharmacokinetic/Pharmacodynamic (PK/PD) relationship
Similar to other beta-lactam antibacterial agents, the time that imipenem concentrations exceed the MIC (T>MIC) hasbeen shown to best correlate with efficacy.
Mechanism of resistance
Resistance to imipenem may be due to the following:

Decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins)
• Imipenem may be actively removed from the cell with an efflux pump.
• Reduced affinity of PBPs to imipenem
•
Imipenem is stable to hydrolysis by most beta-lactamases, including penicillinases and cephalosporinases produced bygram-positive and gram-negative bacteria, with the exception of relatively rare carbapenem hydrolysing beta-lactamases. Species resistant to other carbapenems do generally express co-resistance to imipenem. There is no target-based cross-resistance between imipenem and agents of the quinolone, aminoglycoside, macrolide and tetracyclineclasses.
Breakpoints
The EUCAST MIC breakpoints for imipenem are as follows (v 10.0, valid from 2020-01-01):

1.4.1 Summary of Product Characteristics

Organism Group	Minimum Inhibitory Concentrations (mg/L)	
	Susceptible ≤	Resistant >
Enterobacterales	2	4
Enterobacterales[1] *(Morganella morganii, Proteus* spp. and *Providencia* spp.*)*	0.001	4
Pseudomonas spp.	0.001	4
Acinetobacter spp.	2	4
Staphylococcus spp.	Inferred from cefoxitin susceptibility	
Enterococcus spp.	0.001	4
Streptococcus A, B, C, G	Inferred from the benzylpenicillin susceptibility	
Streptococcus pneumoniae	2	2
Viridans group streptococci	2	2
Haemophilus influenzae	2	2
Moraxalla catarrhalis[2]	2	2
Gram-positive anaerobes except *Clostridioides difficile*	2	4
Gram-negative anaerobes	2	4
Burkholderia pseudomallei	2	2
Non-species related breakpoints[3]	2	4

The intrinsically low activity of imipenem against *Morganella morganii*, *Proteus* spp. and *Providencia* spp. requires the high exposure of imipenem.

Non-susceptible isolates are rare or not yet reported. The identification and antimicrobial susceptibility test result on any such isolate must be confirmed and the isolate sent to a reference laboratory.

Non-species related breakpoint have been determined mainly on the basis of PK/PD data and are independent of Misdistribution's of specific species. They are for use only for species not mentioned in the overview of species-related breakpoints or footnotes.

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

1.4.1 Summary of Product Characteristics

Commonly susceptible species:
Gram-positive aerobes:
Enterococcus faecalis
Staphylococcus aureus (Methicillin-susceptible)*
Staphylococcus coagulase negative (Methicillin-susceptible)
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes

Streptococcus viridans group
Gram-negative aerobes:
Citrobacter freundii
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Moraxella catarrhalis
Serratia marcescens
Gram-positive anaerobes:
*Clostridium perfringens***
Peptostreptococcus spp.**
Gram-negative anaerobes:
Bacteroides fragilis
Bacteroides fragilis group
Fusobacterium spp.
Porphyromonas asaccharolytica
Prevotella spp.
Veillonella spp.
Species for which acquired resistance may be a problem:
Gram-negative aerobes:
Acinetobacter calcoaceticus baumannii complex
Pseudomonas aeruginosa
Inherently resistant species:
Gram positive aerobes:
Enterococcus faecium
Gram negative aerobes:
Some strains of *Burkholderia cepacia* complex
Legionella spp.
Stenotrophomonas maltophilia (formerly *Xanthomonas maltophilia*, formerly *Pseudomonas maltophilia*)

Others:
Chlamydia spp.
Chlamydophila spp.
Mycoplasma spp.
Ureoplasma urealyticum

*

* All methicillin-resistant staphylococci are resistant to imipenem/cilastatin.
** EUCAST non-species related breakpoint is used.

5.2 Pharmacokinetic properties

Imipenem

Absorption

In normal volunteers, intravenous infusion of Implatinze over 20 minutes resulted in peak plasma levels of imipenemranging from 12 to 20 µg/ml for the 250 mg/250 mg dose, from 21 to 58 µg/ml for the 500 mg/500 mg dose, and from 41to 83 µg/ml for the 1000 mg/1000 mg dose. The mean peak plasma levels of imipenem following the 250 mg/250 mg,500 mg/500 mg, and 1000 mg /1000 mg doses were 17, 39, and 66 µg/ml, respectively. At these doses, plasma levels ofimipenem decline to below 1 µg/ml or less in four to six hours.

Distribution

The binding of imipenem to human serum proteins is approximately 20%.

Biotransformation

When administered alone, imipenem is metabolised in the kidneys by dehydropeptidase-I. Individual urinary recoveriesranged from 5 to 40%, with an average recovery of 15-20% in several studies.

Cilastatin is a specific inhibitor of dehydropeptidase-I enzyme and effectively inhibits metabolism of imipenem so thatconcomitant administration of imipenem and cilastatin allows therapeutic antibacterial levels of imipenem to be attainedin both urine and plasma.

Elimination

The plasma half-life of imipenem was one hour. Approximately 70% of the administered antibiotic was recovered intact inthe urine within ten hours, and no further urinary excretion of imipenem was detectable. Urine concentrations ofimipenem exceeded 10 µg/ml for up to eight hours after a 500 mg/500 mg dose of Implatinze. The remainder of theadministered dose was recovered in the urine as antibacterially inactive metabolites, and faecal elimination of imipenemwas essentially nil.

No accumulation of imipenem in plasma or urine has been observed with regimens of PRIMAXIN, administered asfrequently as every six hours, in patients with normal renal function.

Cilastatin

1.4.1 Summary of Product Characteristics

Absorption

Peak plasma levels of cilastatin, following a 20 minute intravenous infusion of Implatinze, ranged from 21 to 26 μg/ml forthe 250 mg/250 mg dose, from 21 to 55 μg/ml for the 500 mg/500 mg dose and from 56 to 88 μg/ml for the 1000mg/1000 mg dose. The mean peak plasma levels of cilastatin following the 250 mg/250 mg, 500 mg/500 mg, and 1000mg/1000 mg doses were 22, 42, and 72 μg/ml respectively.

Distribution

The binding of cilastatin to human serum proteins is approximately 40%.

Biotransformation and elimination

The plasma half-life of cilastatin is approximately one hour. Approximately 70-80% of the dose of cilastatin wasrecovered unchanged in the urine as cilastatin within 10 hours of administration of Implatinze. No further cilastatinappeared in the urine thereafter. Approximately 10% was found as the N-acetyl metabolite, which has inhibitory activityagainst dehydropeptidase comparable to that of cilastatin. Activity of dehydropeptidase-I in the kidney returned to normallevels shortly after the elimination of cilastatin from the blood stream.

Renal insufficiency

Following a single 250 mg/250 mg intravenous dose of Implatinze, the area under the curve (AUCs) for imipenemincreased 1.1-fold, 1.9-fold, and 2.7-fold in subjects with mild (Creatinine Clearance (CrCL) 50-80 ml/min/1.73 m2),moderate (CrCL 30-<50 ml/min/1.73 m2), and severe (CrCL <30 ml/min/1.73 m2) renal impairment, respectively,compared to subjects with normal renal function (CrCL >80 ml/min/1.73 m2), and AUCs for cilastatin increased 1.6-fold,2.0-fold, and 6.2-fold in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjectswith normal renal function. Following a single 250 mg/250 mg intravenous dose of Implatinze given 24 hours afterhaemodialysis, AUCs for imipenem and cilastatin were 3.7-fold and 16.4-fold higher, respectively, as compared tosubjects with normal renal function. Urinary recovery, renal clearance and plasma clearance of imipenem and cilastatindecrease with decreasing renal function following intravenous administration of Implatinze. Dose adjustment isnecessary for patients with impaired

renal function (see section 4.2).

Hepatic insufficiency

The pharmacokinetics of imipenem in patients with hepatic insufficiency have not been established. Due to the limited extent of hepatic metabolism of imipenem, its pharmacokinetics are not expected to be affected by hepatic impairment. Therefore, no dose adjustment is recommended in patients with hepatic impairment (see section 4.2).

Paediatric population

The average clearance (CL) and volume of distribution (Vdss) for imipenem were approximately 45% higher in paediatric patients (3 months to 14 years) as compared to adults. The AUC for imipenem following administration of 15/15 mg/kg per body weight of imipenem/cilastatin to paediatric patients was approximately 30% higher than the exposure in adults receiving a 500 mg/500 mg dose. At the higher dose, the exposure following administration of 25/25 mg/kg imipenem/cilastatin to children was 9% higher as compared to the exposure in adults receiving a 1000 mg/1000 mgdose.

1.4.1 Summary of Product Characteristics

Elderly

In healthy elderly volunteers (65 to 75 years of age with normal renal function for their age), the pharmacokinetics of a single dose of Implatinze 500 mg/500 mg administered intravenously over 20 minutes were consistent with those expected in subjects with slight renal impairment for which no dose alteration is considered necessary. The mean plasma half-lives of imipenem and cilastatin were 91 ± 7.0 minutes and 69 ± 15 minutes, respectively. Multiple dosing has no effect on the pharmacokinetics of either imipenem or cilastatin, and no accumulation of imipenem/cilastatin was observed (see section 4.2)

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity studies.
Animal studies showed that the toxicity produced by imipenem, as a single entity, was limited to the kidney. Co-administration of cilastatin with imipenem in a 1:1 ratio prevented the nephrotoxic effects of imipenem in rabbits and monkeys. Available evidence suggests that cilastatin prevents the nephrotoxicity by preventing entry of imipenem into the tubular cells.
A teratology study in pregnant cynomolgus monkeys given imipenem-cilastatin sodium at doses of 40/40 mg/kg/day(bolus intravenous injection) resulted in maternal toxicity including emesis, inappetence, body weight loss, diarrhoea,abortion, and death in some cases. When doses of imipenem-cilastatin sodium (approximately 100/100 mg/kg/day or approximately 3 times the usual recommended daily human intravenous dose) were administered to pregnant cynomolgus monkeys at an intravenous infusion rate which mimics human clinical use, there was minimal maternal intolerance (occasional emesis), no maternal deaths, no evidence of teratogenicity, but an increase in embryonic loss relative to control groups (see section 4.6).
Long term studies in animals have not been performed to evaluate carcinogenic potential of imipenem-cilastatin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Bicarbonate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Two years.

6.4 Special precautions for storage

Store at temperature not exceeding 30ºC.

6.5 Nature and contents of container

1.4.1 Summary of Product Characteristics

Carton box containing 1,10 or 25 transparent glass (type I) vials, each containing 1080.66 mg powder (according to potency) closed with bromobutyl rubber stopper and sealed with an aluminum / polypropylene plastic cap fitted with a detachable flip top + inner leaflet.

6.6 Special precautions for disposal and other handling

Each vial is for single use only.
Reconstitution:
Contents of each vial must be transferred to 100 ml of an appropriate infusion solution (see sections 6.2 and 6.3): 0.9%sodium chloride. In exceptional circumstances where 0.9% sodium chloride cannot be used for clinical reasons 5%glucose may be used instead.
A suggested procedure is to add approximately 10 ml of the appropriate infusion solution to the vial. Shake well and transfer the resulting mixture to the infusion solution container.
CAUTION: THE MIXTURE IS NOT FOR DIRECT INFUSION.
Repeat with an additional 10 ml of infusion solution to ensure complete transfer of vial contents to the infusion solution. The resulting mixture should be agitated until clear.
The concentration of the reconstituted solution following the above procedure is approximately 5 mg/ml for both imipenem and cilastatin.
Variations of color, from colorless to yellow, do not affect the potency of the product.

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

7. Marketing authorization holder

PHARCO B International

New Borg El Arab - 3rd Industrial Zone, Alexandria-Egypt.

8. Marketing authorization number(s)

34777/2021

9. Date of first authorization/renewal of the authorization

15/07/2021

10. Date of revision of the text

July 2022.