VERAPIME

CEFEPIME HYDROCHLORIDE MONOHYDRATE
Powder and Solvent for Solution for Injection
1g/vial & 2 g/vial

1. DESCRIPTION OF THE MEDICINAL PRODUCT

1.1 Name of the medicinal product: VERAPIME Powder and Solvent for solution for injection 1g/vial & 2g/vial.

1.2 Qualitative and Quantitative composition: Active ingredient: Cefepime Hydrochloride Monohydrate. Excipients: Water for injections. Cefepime Hydrochloride Monohydrate equivalent to Cefepime 1g or 2g.

1.3 Pharmaceutical form: Powder and solvent for solution for Injection.

1.4 Description – Packaging: *Description of powder:* white to pale yellow powder. *Description of solvent:* clear colorless solution. *Description of solution after reconstitution:* clear solution. Verapime 1g/vial is distributed in boxes of 1, 10 and 50 glass vials containing 1g of Cefepime and it is packed in carton boxes along with 1, 10 or 50 plastic ampoules of 3ml Water for Injections, respectively. Verapime 2g/vial is distributed in boxes of 1, 10 and 50 glass vials containing 2g of Cefepime and it is packed in carton boxes along with 1, 10 or 50 plastic ampoules of 10ml Water for Injections, respectively. Not all pack sizes may be marketed.

1.5 Pharmacological properties: ATC CODE: J01DA24

1.6 Marketing Authorization Holder: Pharmaforte (M) Sdn. Bhd., 2, Jalan PJU 3/49, Sunway Damansara 47810 Petaling Jaya, Selangor Malaysia.

2. WHAT YOU SHOULD KNOW ABOUT THE MEDICINE YOUR DOCTOR HAS PRESCRIBED TO YOU

2.1 General information

2.1.1 Pharmacodynamic properties: Microbiology: Verapime is a bactericidal agent that has a broad spectrum of activity against a wide range of gram-positive and gram-negative bacteria including most strains resistant to aminoglycosides or 3rd-generation cephalosporins (eg, ceftazidime). It is highly resistant to hydrolysis by most b-lactamases, and has low affinity for chromosomally-encoded b-lactamases, and exhibits rapid penetration into gram-negative bacterial cells.

Verapime has been shown to be bactericidal by time-kill analysis (killing-curves) and by determination of minimum bactericidal concentrations (MBC) for a wide variety of bacteria.

The cefepime MBC/MIC ratio was less than or equal to 2 for >80% of isolates of all gram-positive and gram-negative species tested. Synergy with aminoglycosides has been demonstrated *in vitro*, primarily with *Pseudomonas aeruginosa* isolates.

Verapime is active against most strains of the following organisms:

Gram-Positive Aerobes: *Staphylococcus aureus* (including b-lactamase-producing strains), *Staphylococcus epidermidis* (including b-lactamase-producing strains), other staphylococci including *S. hominis* and *S. saprophyticus, Streptococcus pyogenes* (Group A streptococci), *Streptococcus agalactiae* (Group B streptococci), *Streptococcus pneumoniae* (including intermediate penicillinresistant strains with penicillin MIC of 0.1-1 mcg/mL), other b-hemolytic streptococci (Group C, G, F), *S. bovis* (Group D), Streptococci viridans.

(Most strains of enterococci eg, *Enterococcus faecalis* and methicillin-resistant staphylococci are resistant to most cephalosporins including Verapime.)

Gram-Negative Aerobes: *Pseudomonas* sp (including *P. aeruginosa, P. putida, P. stutzeri*), *Escherichia coli, Klebsiella* sp (including *K. pneumoniae, K. oxytoca, K. ozoaenae*), *Enterobacter* sp (including *E. cloacae, E. aerogenes, E. agglomerans, E. sakazakii*), *Proteus* sp (including *P. mirabilis, P. vulgaris*), *Acinetobacter calcoaceticus* (subspecies *anitratus, lwoffi*), *Aeromonas hydrophila, Capnocytophaga* and *Citrobacter* spp (including *C. diversus, C. freundii*), *Campylobacter jejuni, Gardnerella vaginalis, Haemophilus ducreyi, Haemophilus influenzae* (including b-lactamase-producing strains), *Haemophilus parainfluenzae, Hafnia alvei, Legionella* sp, *Morganella morganii, Moraxella catarrhalis* (*Branhamella catarrhalis*, including b-lactamase-producing strains), *Neisseria gonorrhoeae* (including b-lactamase-producing strains), *Neisseria meningitidis, Providencia* sp (including *P. rettgeri, P. stuartii*), *Salmonella* sp, Serratia (including *S. marcescens, S. liquefaciens*), *Shigella* sp and *Yersinia enterocolitica*.

Note: Verapime is inactive against many strains of *Stenotrophomas maltophilia (Pseudomonas maltophilia*).

Anaerobes: *Bacteroides* sp, *Clostridium perfringens, Fusobacterium, Mobiluncus, Peptostreptococcus, Prevotella melaninogenica* and *Veillonella* spp.

Note: Verapime is inactive against *Bacteroides fragilis* and *Clostridium difficile*.

Susceptibility Testing: Laboratory reports with standardized single-disk susceptibility results using a 30mcg cefepime disk should be interpreted according to the following criteria: See Table 1.

Table 1.

Zone Diameter (mm)	Interpretation
≥ 18	(S) Susceptible
15-17	(I) Intermediate
≤14	R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood concentrations. A report of "Intermediate" indicates that the organism would be susceptible when high dosage is used or when the infection is confined to tissues and fluids (eg, interstitial fluid and urine) in which high antibiotic levels are attained. A report of "Resistant" indicates that the achievable concentration of the antibiotic is unlikely to be inhibitory and other therapy should be selected.

Organisms should be tested with the cefepime disk because cefepime has been shown to be active *in vitro* against certain strains found to be resistant with other b-lactam disks. The cefepime disk should not be used for testing susceptibility to other cephalosporins. Standardized quality control procedures require the use of control organisms.

Dilution Techniques: Using standardized dilution methods or an equivalent (eg, E-test), the MIC values obtained should be interpreted according to the following criteria: See Table 2.

Table 2.

MIC (mcg/mL)	Interpretation
≤8	(S) Susceptible
16	(I) Intermediate
≤32	R) Resistant

As with diffusion techniques, dilution techniques require the use of laboratory control organisms

2.1.2 Pharmacokinetic properties: Cefepime follows linear pharmacokinetics for dosage limits 250 mg- 2 g (IV) and 500 mg- 2 g (IM).

Absorption: After IM administration, absorption is rapid and complete.

Distribution: Average plasma concentrations of Cefepime observed in healthy adult males following single 30 minutes infusions of 250 mg, 500 mg, 1 g, 2 g or intramuscular injections of 500 mg, 1g and 2g are summarised in table 3. Cefepime concentrations achieved in specific tissues and body fluids are displayed in table 4.

Table 3: Mean plasma concentrations of Cefepime (mg/mL) in healthy adult males

Cefepime dose	0.5 hr	1 hr	2 hr	4 hr	8 hr	12 hr
250 mg IV	20.1	10.9	5.9	2.6	0.5	0.1
500 mg IV	38.2	21.6	11.6	5.0	1.4	0.2
1g IV	78.7	44.5	24.3	10.5	2.4	0.6
2g IV	163.1	85.8	44.8	19.2	3.9	1.1
500 mg IM	8.2	12.5	12.0	6.9	1.9	0.7
1g IM	14.8	25.9	26.3	16.0	4.5	1.4
2g IM	36.1	49.9	51.3	31.5	8.7	2.3

Table 4: Mean concentrations of Cefepime in body fluids & tissues in healthy adult males

Tissue or fluid	Dose & Route of Administration	Average time of sample post-dose (hr)	Mean concentration in tiss ue (µg/g) or body fluid (µg/ml)
Urine	500mg IV	0 - 4	292
	1g IV	0 - 4	926
	2g IV	0 - 4	3120
Bile	2g IV	9.4	17.8
Peritoneal fluid	2g IV	4.4	18.3
Blister fluid	2g IV	1.5	81.4
Bronchial	2g IV	4.8	24.1
Sputum	2g IV	4.0	7.4
Prostate	2g IV	1.0	31.5
Appendix	2g IV	5.7	5.2
Gallbladder	2g IV	8.9	11.9

The distribution of Cefepime in tissues does not display fluctuations within the dosage regimen of 250 mg- 2 g. The mean volume of distribution during steady state is 18 litres. Cefepime elimination half-life is two hours on average. There is no evidence of accumulation in individuals who received two IV every 8 hours within a period of 9 days. Serum protein binding of Cefepime is less than 19% and is independent of serum Cefepime concentration.

Metabolism: Cefepime is minimally metabolised. It is converted to N- oxide of N-methylpyrrolidine, which is excreted in the urine in a quantity equivalent to 7% of the administered dose.

Elimination: Total body clearance averages 120 ml/min. The average renal clearance of Cefepime is 110 ml/min. It is eliminated almost exclusively by renal mechanisms, primarily glomerular filtration. Urinary recovery of unchanged Cefepime accounts for approximately 85% of the administered dose. After administration of a 500 mg dose IV, Cefepime concentrations are no longer detectable after 12 hours in the plasma and after 16 hours in the urine. Cefepime concentration in the urine averages 17.8 mg/ml, 16 hours after administration. After administration of 1 g or 2 g IV, the average concentrations in the urine are 26.5 and 28.8 mg/ml respectively, after 12-24 hours. Plasma concentration levels are not detectable after 24 hours.

Geriatric Patients: Cefepime distribution was studied in geriatric patients (aged > 65 years). It was observed that no dosage adjustments are required in geriatric patients, whose renal function is normal. Dose adjustments are recommended in geriatric patients, if renal function is compromised.

Patients with hepatic impairment: Cefepime pharmacokinetics are not altered in patients with hepatic impairment to whom a single dose of 1g is administered. No adjustment of dosage is hence needed.

Patients with renal impairment: Studies carried out on patients with various degrees of renal impairment have shown significant prolongment of elimination half-life. There is a linear relationship between renal elimination of Cefepime and creatinine clearance in patients with renal impairment. The average half-life in patients requiring dialysis therapy (haemodialysis or continuous ambulatory peritoneal dialysis is 13-17 hours.

Paediatric patients: Cefepime pharmacokinetics with single or multiple doses were evaluated in patients aged between 2 months and 16 years, who received doses of 50 mg/kg by intravenous infusion or by intramuscular administration. Multiple doses were administered every 8 or 12 hours for at least 48 hours. Average plasma concentrations of Cefepime after the first dose were similar to those at steady state, with a slight accumulation only observed after multiple dosing. Steady state intramuscular administration resulted in average maximum plasma concentrations of Cefepime of about 68 mg/ml, observed within 0.75 hours. The average minimum concentration after steady state intramuscular administration was 6.0 mg/ml within 8 hours. Bioavailability averaged 82% after intramuscular administration. Other pharmacokinetic parameters were unaltered in infants and children, according to measurements carried out between the first dose and the steady state condition, regardless dosage regimen (intervening periods of 12 or 8 hours). Furthermore, no pharmacokinetic differences were observed between patients of different age or between male and female patients. After a single intravenous dose, total clearance averaged 3.3 ml/min/kg and the average distribution volume was 0.3 L/kg. Total average elimination half-life was 1.7 hours. Urinary recovery of unchanged Cefepime was 60.4% of the administered dose and renal clearance was the primary elimination pathway averaging 2.0 ml/min/kg. Cefepime concentrations in the cerebrospinal fluid compared to plasma concentrations are presented in table 5:

Table 5: Average Cefepime plasma (PL) and cerebrospinal fluid (CSF) concentrations and ratio of CSF/PL in infants and children

Sampling time (hr)	N	Plasma (PL) concentration (mg/ml)	Cerebrospinal fluid (CSF) concentration (mg/ml)	Ratio CSF/PL
0.5	7	67.1 (51.2)	5.7 (7.3)	0.12 (0.14)
1	4	44.1 (7.8)	4.3 (1.5)	0.10 (0.04)
2	5	23.9 (12.9)	3.6 (2.0)	0.17 (0.09)
4	5	11.7 (15.7)	4.2 (1.1)	0.87 (0.56)
8	5	4.9 (5.9)	3.3 (2.8)	1.02 (0.64)

*****Patients aged between 3.1 months and 14.7 years, with an average (SD) age of 2.9 (3.9) years. Patients with suspected central nervous system infection received treatment with 50 mg/kg of Cefepime, administered as intravenous infusion of 5-20 min every 8 hours. Plasma and CSF samples were taken from the selected patients in sampling times relevant to infusion end time on the day 2 or 3 of the treatment.

2.2 Therapeutic Indications: Treatment of the following infections when caused by susceptible strains of bacteria: Lower respiratory tract infections (including pneumonia and bronchitis), urinary tract infections (both complicated, including pyelonephritis and uncomplicated infections), skin and skin structure infections; intra-abdominal infections (including peritonitis and biliary tract infections), gynecologic infections, septicemia, empiric treatment in febrile neutropenic patients. In pediatric patients for treatment of infections when caused by susceptible bacteria: Pneumonia, urinary tract infections (both complicated and uncomplicated, including pyelonephritis), skin and skin structureinfections, septicemia, empiric treatment in febrile neutropenia.

2.3 Contraindications: Known hypersensitivity to Cefepime, cephalosporines, penicillines, other lactam antibiotics or L-Arginine, which is an excipient of this medicine.

2.4 Special warnings and precautions for use: Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with Verapime, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapanems or other beta-lactam agents. If an allergic reaction occurs, Verapime must be discontinued immediately and appropriate alternate therapy instituted.

In patients with impaired renal function, such as reduction of urinary output because of renal insufficiency (creatinine clearance ≤60 ml/min) or other conditions that may compromise the renal function, the dosage of VERAPIME should be adjusted to compensate for the slower rate of renal elimination. Since high and prolonged concentrations of the antibiotic in the serum may occur after normal dosage in patients with renal insufficiency or under other conditions that may compromise the renal function, the maintenance dose should be reduced when VERAPIME is administered to these patients. Post treatment should be defined by the degree of renal impairment, the severeness of the infection and the susceptibility of the causative microorganism. Serious adverse events, including encephalopathy (consciousness disorders, including confusion, hallucinations, lethargy and coma), myoclonus, seizures (including non convulsive epilepsy) and/or renal failure seizures, have been reported in post-marketing experience. Most of the cases were reported in patients with renal impairment who received doses higher than the recommended. In general, nephrotoxicity symptoms were eliminated after discontinuation of Cefepime and/or after dialysis, nevertheless in some cases they were lethal. The appearance of any allergic symptoms requires discontinuation of the treatment.Before therapy with cephalosporines is instituted, careful history inquiry should be made to the patient. Due to potential allergic cross-reactions between cephalosporines and penicillins in 5-10% of cases, cephalosporines should be administered with caution to patients sensitive to penicillins. Close monitoring of these patients is required from the first dose. The use of cephalosporines in patients with history of acute allergic reaction to cephalosporines is completely contraindicated. If there is any doubt, it is necessary that the physician is present during the first administration of the drug to the patient in order to manage any potential allergic reaction. Serious hypersensitivity reactions may require epinephrine and other supportive therapy. Pseudomembranous colitis has been reported with all broad-spectrum antibiotics including Cefepime; therefore, it is important to consider this diagnosis in patients who develop diarrhoea in association with the use of antibiotics. Mild cases of colitis may respond to drug discontinuation alone. In moderate to severe cases, management may require special treatment. Renal function should be monitored carefully if drugs with nephrotoxic potential, such as aminoglycosides or diuretics are administered with VERAPIME. As with other antibiotics, prolonged use of VERAPIME may result in overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken. Arginine is not recommended for patient following a heart attack.

Elderly patients: More than 6,400 adults received Cefepime in clinical trials, 35% of whom were aged 65 or above and 16% were aged 75 or above. In clinical trials, where elderly patients received the typical recommended dose in adults, the clinical efficacy and safety was comparable to the clinical efficacy and safety in non-geriatric adult patients, except for patients with renal impairment. There was a small prolongment in elimination half life and lower renal clearance values compared to those seen in younger patients. Dosage adjustments are recommended if renal function is compromised. Since elderly patients are more likely to present with renal

impairment, the dosage choice must be made with caution and renal function should be monitored. Severe adverse effects, including encephalopathy (consciousness disorders, including confusion, hallucinations, lethargy and coma), myoclonus, seizures (including non-convulsive epilepsy), and/or renal failure were presented in patients with renal impairment to whom the usual dose of Cefepime was administered.

2.5 Pregnancy and Lactation: Reproduction studies in mice, rats and rabbits did not indicate damage to the foetus. There are not sufficient and well-controlled studies in pregnant women. Since reproduction studies do not always make provisions for human response, this drug should be administered during pregnancy only if it is absolutely necessary. Cefepime is excreted in human breast milk in very low concentrations. Therefore caution is required when VERAPIME is administered to nursing mothers.

2.6 Effects on ability to drive and use machines: There are no data regarding the effect of VERAPIME on the ability to drive.

2.7 Interaction with other medicinal products and other forms of interaction: The pharmacokinetics of cefepime and amikacin when given concurrently to patients with normal renal function do not appear to be altered. Concomitant administration of probenecid prolongs the renal tubular secretion of cephalosporins resulting in high serum concentrations of these antibiotics.

2.8 Posology and method of administration

VERAPIME can be administered intravenously by a slow (3-5 min) intravenous injection, or through an infusion device, or directly in the infusion fluid (1g, 2 g). It can also be administered intramuscularly, by deep intramuscular injection (1g).

Adults: The recommended dosage schemes, when administered in monotherapy (IV or IM), are summarised in table 6.

Preoperative prevention in adults: The recommended dose for the prevention of infections in patients submitted to colon or rectus operations is as follows: Single intravenous dose 2g administered 60 minutes before the operation. A single intravenous dose of 500mg metronidazole should be administered immediately after the completion of the infusion of VERAPIME. The dose of metronidazole must be prepared and administered accordingly to the official instructions into force as those are prescribed in its instructions for administration. Because of the incompatibility between Cefepime and metronidazole, the two substances should not be mixed in the same container. After Cefepime is administered it is recommended that the intravenous administration set is flushed with a compatible fluid, before metronidazole is infused. If the operation lasts more than 12 hours after the time of the initial preventive VERAPIME dose administration, then a second dose of the product must be administered, followed by metronidazole, 12 hours after the initial preventive dose.

Table 6: Recommended dosage

Type of infection	Dose and route of administration	Dosing frequency
Non complicated pyelonephritis	1g IV or IM	Twice daily
Severe hospital infections such as septicaemia/ bacillaemia, pneumonia, complicated urinary tract infections & biliary tract infections.	2g IV	Twice daily
Severe hospital infections due to Pseudomonas	2g IV	Thrice daily
*Febrile incidents in neutropenic patients**	2g IV	Thrice daily
* Cefepime has been successfully used either as monotherapy or in combination with an aminoglycoside or a glycopeptide		

Children (aged 2 months to 12 years, with normal renal function):

Typically recommended dosage regimens: *Pneumonia, Urinary Tract Infections:* In patients older than 2 months and with bodyweight ≤ 40 kg: 50 mg/kg every 12 hrs for 10 days. For more severe infections, a dosage regimen of every 8 hours may be used. *Septicaemia, bacterial meningitis and empiric treatment in neutropenic patients:* In patients older than 2 months and with bodyweight ≤ 40 kg: 50 mg/kg every 8 hours for 7-10 days. There is little experience with VERAPIME administration in paediatric patients younger than 2 months. In paediatric patients with bodyweight > 40 kg, the dosage regimen recommended for adults should be used (see table of dosage in adults). In patients older than 12 years, whose weight is ≤ 40 kg, the recommended dosage regimens for children with weight ≤ 40 kg should be used. The dosage in paediatric patients should not exceed the maximum dosage for adults (2g every 8 hours). There is little experience of intramuscular administration of the drug in paediatric patients.

Adult patients with impaired renal function: In patients with renal impairment, the dose of VERAPIME should be regulated so as to compensate for the lower rate of renal clearance. The recommended initial dose of VERAPIME in patients with mild to moderate renal function impairment should be the same as in patients with normal renal function. The recommended maintenance doses of VERAPIME in adult patients with renal insufficiency are presented in the following table. Only if concentration of creatinine in serum (SC) is available, the *Cockcroft and Gault* equation may be used to estimate creatinine clearance. The serum creatinine should represent the steady state of renal function:

$$\text{Creatinine clearance (ml/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{SC (mg/dL)}}$$

The above equation applies for male patients. For female patients, creatinine clearance equals the 0.85 of creatinine clearance, as calculated above for male patients.

Maintenance dosing schedule in adult patients with renal impairment

Creatinine clearance (mL/min)	Recommended maintenance dose			
	Usual dosage, no adjustment is required			
> 60	2g every 8 hrs	2g every 12 hrs	1g every 12 hrs	500mg every 12 hrs
30 - 60	2g every 12 hrs	2g every 24 hrs	1g every 24 hrs	500mg every 24 hrs
11 - 29	2g every 24 hrs	1g every 24 hrs	500mg every 24 hrs	500mg every 24 hrs
≤ 11	1g every 24 hrs	500mg every 24 hrs	250mg every 24 hrs	250mg every 24 hrs
Haemodialysis*	500mg every 24 hrs	500mg every 24 hrs	500mg every 24 hrs	500mg every 24 hrs

*A pharmacokinetic model shows that reduced dosage for these patients is necessary. Patients who receive VERAPIME and undergo haemodialysis need to adjust the dose as follows: 1 g attack dose on the first day of treatment with Cefepime and 500 mg every day on the following days. On the day of dialysis, VERAPIME should be given at the completion of each dialysis session. Whenever it is possible, VERAPIME should be administered at the same time every day.

Haemodialysis patients: In patients undergoing haemodialysis, approximately 68% of the total amount of Cefepime present in the body at the start of dialysis is removed during a 3-hour dialysis session. In patients undergoing continuous ambulatory peritoneal dialysis, VERAPIME may be administered at the same doses recommended for patients with normal renal function, ie. 500 mg, 1g or 2g, depending on infection severity, at a dosage interval of every 48 hours.

Children with impaired renal function: There are not enough data in paediatric patients with renal insufficiency, however since pharmacokinetics are similar to those in adults, it is presumed that in paediatric patients Cefepime is primarily excreted from the reins and therefore in paediatric patients aged above 2 months and up to 12 years with renal impairment, dosage adjustment should be considered.As illustrated in the table referring to adult patients with renal insufficiency, the same increase between the doses and/or the dose decrease should apply. When only serum creatinine (SC) is available, creatinine clearance may be estimated based on one of the two following equations:

$$\text{Creatinine clearance (ml/min/1.73m}^2\text{)} = \frac{0.55 \times \text{Height (cm)}}{\text{Serum creatinine (mg/dL)}}$$

$$\text{Creatinine clearance (ml/min/1.73m}^2\text{)} = \frac{0.52 \times \text{Height (cm)} - 3.6}{\text{Serum creatinine (mg/dL)}}$$

Patients with impaired hepatic function: No adjustment is necessary for patients with impaired hepatic function.

2.10 Overdose: In case of overdosage, especially in patients with compromised renal function, haemodialysis will aid in the removal of Cefepime from the body; peritoneal dialysis is of no value. Accidental overdosing may occur if large doses are given to patients with reduced renal function.

2.11 Undesirable effects: Cefepime is generally well tolerated.

Undesirable effects occurred at an incidence of > 0.1% - 1% (unless otherwise stated): *Hypersensitivity reactions:* rash (1.8%), pruritus, urticaria. *Gastrointestinal system:* nausea, vomiting, oral moniliasis, diarrhoea (1.2%), colitis (including pseudomembranous colitis). *Central nervous system:* headache. Other: fever, vaginitis, erythema

Undesirable effects occurred between 0.05%-0.1%: abdominal pain, constipation, vasodilation, dyspnoea, dizziness, paraesthesia, genital pruritis, taste perversion, chills and unspecified moniliasis.

Undesirable effects occurred at an incidence of <0.05%: anaphylaxis and seizures.

Laboratory test abnormalities that developed during clinical trials in patients with normal baseline values were transient. Those that occurred at a frequency between 1% and 2% (unless stated otherwise) were elevations in alanine aminotransferase (3.6%), aspartate aminotransferase (2.5%), alkaline phosphatase, total bilirubin, anaemia, eosinophilia, prolonged prothrombin time, partial thromboplastin time (2.8%) and positive Coombs' test without haemolysis (18.7%). Transient elevations of blood urea nitrogen and/or serum creatinine and transient thrombocytopenia were observed in 0.5% to 1% of patients. Transient leucopenia and neutropenia were also observed (< 0.5%).

Paediatric Patients: The safety profile of Cefepime in infants and children is similar to that of adults. The most common undesirable effect associated with the administration of Cefepime was rash.

2.12 List of excipients: L-Arginine. *Diluent:* Water for Injections.

2.13 Incompatibilities: Should not be mixed with other medicinal products in the same syringe or infusion flask.

2.14 Shelf life: 36 months at temperature ≤30°C. After reconstitution: 12 hours at temperature ≤25°C or 24 hours at temperature 2°-8°C.

2.15 Special precautions for storage: Store at temperature below 30°C and keep protected from light. The reconstituted solution is stable (2-8°C) for 24 hours if refrigerated or 12 hours at room temperature.

2.16 Instructions for use and handling:

Intravenous Administration: VERAPIME can be reconstituted with Water for Injections or any other compatible diluent.

Strength	Volume of diluent to be added (ml)	Approximate available final volume (ml)	Approximate concentration (mg/ml)
1g IM	3.0	4.4	240
1g IV	10.0	11.4	90
2g IV	10.0	12.8	160

Reconstituted solutions for intravenous administration can be administered directly by slow intravenous injection (3-5 min) or by infusion device or directly in the infusion fluid.

Intramuscular Administration: For the reconstitution of 1g VERAPIME, Water for Injections or 0.5% or 1% Lidocaine Hydrochloride is used.

2.17 Compatibility: VERAPIME is compatible with the following infusion solutions: 0.9% Sodium Chloride (with or without Dextrose 5%), Dextrose 5% or 10%, Lactated Ringers solution (with or without Dextrose 5%), M/6 solution of Sodium lactate.

VERAPIME can be administered concurrently with other antibiotics, provided that not the same syringe or infusion device or the same injection site is used. As with other cephalosporines, the colour of VERAPIME solution after reconstitution may become yellowish on storage, product potency is nonetheless unaffected.

2.18 Date of revision of the text: April 2019

3. GENERAL INFORMATION FOR THE RATIONAL USE OF MEDICINES

- Read this entire leaflet carefully before you start taking this medicine. It contains important information for you.
- Keep this leaflet. You may need to read it again.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you need more information or advice about your medicine, ask your doctor or pharmacist.
- Always take this medicine exactly as your doctor has told you in order to get the best results from it.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
- Do not keep your medicines in bathroom medicine cabinets because heat and humidity can affect their quality. Always keep your medicines in the original container and in a cool and dry place.
- Do not keep medicines that you no longer use or that have already expired.
- Keep all medicines out of the reach and sight of children.

4. GENERAL CLASSIFICATION FOR SUPPLY

For hospital use only.

Reg. No.-Verapime 1g: MAL10120018AZ

Reg. No.-Verapime 2g: MAL10120019AZ

DEMO S.A.
Pharmaceutical Industry
21st km National Road Athens-Lamia,
14568 Krioneri, Attiki, Greece.
Tel. + 30 210 8161802, Fax: + 30 210 8161587.