For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Cefepime and Sulbactam for Injection Along with Solvent

SUPIME for IM / IV Use

DESCRIPTION

SUPIME is an Antibiotic Adjuvant Entity (AAE) comprising of cefepime hydrochloride, a fourth generation cephalosporin, sulbactam sodium, a beta-lactamase inhibitor and a non-antibiotic adjuvant L-arginine. It is available as sterile, dry powder for reconstitution before use.

Cefepime hydrochloride, is a semi-synthetic, broad spectrum antibiotic for parenteral administration. Cefepime hydrochloride is a white to pale yellow powder and a molecular weight of 571.5 g/moL. It is highly soluble in water. Sulbactam sodium is a derivative of basic penicillin nucleus. It is an irreversible ß-lactamase inhibitor. The molecular weight is 255.22 g/mol. It contains 92 mg sodium per gram. L-arginine, at an approximate concentration of 72.5% of cefepime is added as excipient. Supime is supplied for intramuscular and intravenous administration in strengths of 1.5 g and 3.0 g. It is packaged in tubular glass vials.

Each 1.5 g vial of Supime contains: Cefepime Hydrochloride I.P. equivalent to Cefepime 1000 mg and Sulbactam Sodium I.P. equivalent to Sulbactam 500 mg

Each 3.0 g vial of Supime contains: Cefepime Hydrochloride I.P. equivalent to Cefepime 2000 mg and Sulbactam Sodium I.P. equivalent to Sulbactam 1000 mg.

Solvent for Injection: Sodium Chloride I.P. 1 mg, Water for Injections I.P. q.s.

CLINICAL PHARMACOLOGY

Mechanism of action: Supime containing cefepime is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. Sulbactam is an irreversible ß-lactamase inhibitor which binds the ß-lactamase enzyme and does not allow it to interact with the antibiotic, thus extending their spectrum of activity. It has maximum activity against CTX-M (Cefotaxime resistant β-lactamases gene) type of class A ß-lactamases and moderate activity against TEM-β-lactamases gene & SHV-β-lactamases gene. It does not induce the production of AmpC type class C beta- lactamases.

Sulbactam not only potentiates the antibacterial activity by inhibiting beta-lactamases, but also exhibits a moderate antibacterial activity by forming a protein complex with beta-lactamases. Thus, sulbactam addition extends the spectrum of activity of cefepime target sites.

MICROBIOLOGY

Cefepime and sulbactam act synergistically and have a broad spectrum of in vitro activity that encompasses a wide range of gram positive and gram negative bacteria. Cefepime and sulbactam combination has been shown to be active against ESBL strains of the following bacteria.

Aerobes (Gram-negative bacteria): Enterobacter, *Escherichia coli, Klebsiella pneumoniae, Proteus sp.* (including indole-positive and indole-negative, Proteus mirabilis*), Pseudomonas aeruginosa, Acinetobacter calcoaceticus subsp. woffii, Citrobacter diversus, Citrobacter freundii, Enterobacter agglomerans, Haemophilus influenzae, Hafnia alvei, Klebsiella oxytoca, Moraxella catarrhalis,Morganella morganii, Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Serratia marcescens, Neisseria meningitidis.*

Aerobes (Gram-positive bacteria*):* *Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus pneumoniae, Streptococcus pyogenes* (Lancefield's Group A streptococci), *Staphylococcus epidermidis* (methicillin-susceptible isolates only), *Staphylococcuss aprophyticus, Streptococcus agalactiae* (Lancefield's Group B streptococci).

Anaerobes (Gram-negative bacteria): *Bacteroides fragilis, Citrobacter diversus, Citrobacter freundil, Providencia species, Salmonella species (including S. typhi), Shigella species.*

Anaerobes (Gram-positive bacteria): *Peptostreptococcus species & Clostridium species.*

The combination agent is useful in the treatment of moderate to severe infections particularly when a ESBL microbial aetiology is suspected or documented. In addition, sulbactam itself has the highest intrinsic activity against the opportunistic pathogen, *Acinetobacter baumannii.*

In addition Sulbactam, has several advantages over tazobactam. Sulbactam binds with plasmid mediated and chromosomal mediated beta-lactamases produced by Enterobacteriaceae, whereas tazobactam binds with only plasmid mediated beta-lactamases produced by Enterobacteriaceae. Sulbactam displayed highest interaction energy in docking study against CTM-X class of beta-lactamases, whereas tazobactam displayed less interaction energy in docking study against CTM-X class of beta-lactamases. Sulbactam has higher intrinsic bacteriostatic property against Bacteroides spp., Acinetobacter spp., and N. gonorrhoeae than tazobactam.

SUSCEPTIBILITY TESTS

Dilution techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds.

Diffusion techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. This procedure uses paper disks impregnated with 30 μg of cefepime and 15 μg of sulbactam to test the susceptibility of microorganisms to Supime.

Table 1: Breakpoint for Supime against >500 resistant clinical isolates.

Pathogens	Minimum inhibitory concentration (µg/mL)			Disk diffusion (Zone diameter in mm)		
	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
Enterobacteriaceae	≤4	8-16	≥32	≥22	18-21	≤17
Pseudomonas spp.	≤8	16	≥32	≥18	15-17	≤14
Non-*Enterobacteriaceae*	≤8	16	≥32	≥18	15-17	≤14

PHARMACOKINETICS

Absorption & bioavailability: In Supime cefepime is almost completely absorbed through IM administration. Peak serum concentrations are attained within 1.4–1.6 h.

Healthy volunteers: The average plasma concentrations of cefepime after Supime administration observed in healthy adult male volunteers (n=9) at various times following single 30 minute infusions (IV) of cefepime 1 g and 2 g are summarized in Table 2. Cefepime pharmacokinetics is linear and dose dependent and there is no evidence of accumulation in healthy adult male volunteers.

Table 2: Average plasma concentrations in mcg/mL of Cefepime and Sulbactam pharmacokinetic parameters (± SD) through intravenous administration and intramuscular administration.

Drug	Dose Level	Intravenous administration [Cefepime (µg/mL)]					Intramuscular administration [Cefepime (µg/mL)]				
		0.5 h	1 h	12 h	Cmax	AUC	0.5 h	1 h	12 h	Cmax	AUC
Cefepime	1.0g	78.7	44.5	0.6	84.09	172.44	14.8	25.9	1.4	29.6	137
	2.0g	163.1	85.8	0.98	163.9	284.8	36.1	49.9	2.3	57.5	262
Drug	**Dose Level**	**Intravenous administration [Sulbactam (µg/mL)]**					**Intramuscular administration [Sulbactam (µg/mL)]**				
		0.5 h	**1 h**	**12 h**	**Cmax**	**AUC**	**0.5 h**	**1 h**	**12 h**	**Cmax**	**AUC**
Sulbactam	500mg	19.57	13.86	0.02	19	28.79	10.61	14.03	0.0001	14.2	35.5
	1000mg	39.14	27.72	0.01	39.14	57.42	24.5	32.39	0.0002	32.44	67.4

Distribution: Cefepime in Supime is widely distributed into tissues and fluids, including blister fluid, bronchial mucosa, sputum, bile, peritoneal fluid, appendix, gallbladder, CSF, prostate and milk. The average steady-state volume of distribution of cefepime is 18±2 L and sulbactam is 18-27.6 L. The serum protein binding of cefepime is around 20% and is independent of its concentration in serum. Sulbactam has been found to be approximately 38% reversibly bound to human serum protein. Sulbactam sodium is well distributed into fluids and tissues following an IM or IV administration. Sulbactam is found in peritoneal fluid, blister fluid, tissue fluid, sputum, middle ear effusion, intestinal mucosa, bronchial wall, alveolar lining fluid, sternum, pericardium, myocardium, endocardium, prostate, gallbladder, bile, myometrium, salpinges, ovaries & appendix.

Metabolism: Cefepime is metabolized in vivo to N-methylpyrrolidine (NMP) which is rapidly converted to the N-oxide (NMP-N-oxide). Sulbactam is not metabolized in the body.

Elimination: After Supime administration, 70-80% cefepime is eliminated as an unchanged active substance in the urine by glomerular filtration, whilst the remainder is excreted via the bile in to the faeces as microbiologically inactive metabolites. Elimination of cefepime is principally via renal excretion with an average (±SD) half-life of 2 (±0.3) h and total body clearance of 120 (±8) mL/min in healthy volunteers. <1% of the dose eliminated as NMP, 6.8% as NMP-N-oxide and 2.5% as an epimer of the drug. Patients with renal dysfunction and patients undergoing haemodialysis require dosage adjustment. Sulbactam reaches its half-life in 0.94 h and it is excreted primarily in the urine (glomerular filtration and tubular secretion) with a small amount being recovered in bile and faeces.

SPECIAL POPULATIONS

Renal impairment: Cefepime pharmacokinetics investigated in 30 patients with various degrees of renal impairment showed that the average half-life in patients requiring haemodialysis was 13.5 (±2.7) h and in patients requiring continuous peritoneal dialysis was 19 (±2) h. Cefepime total body clearance decreased proportionally with creatinine clearance in patients with abnormal renal function, which serves as the basis for Supime dosage adjustment recommendations in this group of patients.

Hepatic impairment: The pharmacokinetics of cefepime were unaltered in patients with hepatic impairment who received a single 1.5 g dose of Supime.

Geriatric patients: Cefepime pharmacokinetics have been investigated in elderly (65 years of age and older) men and women whose mean (SD) creatinine clearance was 74 (±15) mL/min. There appeared to be a decrease in cefepime total body clearance as a function of creatinine clearance. Therefore, dosage administration of Supime in the elderly should be adjusted as appropriate if the patient's creatinine clearance is 60 mL/min or less.

INDICATIONS

Mainly for the treatment of lower respiratory tract infections (LRTI; Nosocomial and community acquired pneumonia), uncomplicated and complicated urinary tract infections (UTI; including pyelonephritis) and mild to moderate bacterial septicaemia.

Additional indications: Skin and skin structure infections and severe/complicated intra-abdominal infections (including peritonitis and gallbladder infection).

DOSAGE AND ADMINISTRATION

Dosage: Supime Injection is available in 1.5 g and 3 g strengths. It is administered as twice or thrice a day in equally divided doses depending on the type and severity of infection. Maximum daily dose up to 9 g. Dosage regimen of cefepime and sulbactam combination should be adjusted in patients with marked decrease in renal function (creatinine clearance of less than 30 mL/min) to

compensate for the reduced clearance of cefepime and sulbactam. The status of renal function should be estimated by measurement of serum creatinine concentration or calculation of the creatinine clearance rate. It is desirable to measure both peak and trough serum concentrations intermittently during therapy.

When only serum creatinine is available, the following formula (based on sex, weight and age of the patient) may be used to convert this value in to creatinine clearance.

Males: Weight in (kg) x (140 - age) / 72 x Serum creatinine

Females: (0.85) x (above value)

Table 3: Preparation of Solutions of Supime

Single Dose Vials for Intravenous/ Intramascular Administration	Amount of Diluent to be added (ml)	Approximate Available Volume (ml)	Approximate cefepime and sulbactam concentration (mg/ml)
0.75g (IV)	5.0	5.9	80/40
0.75g (IM)	1.5	2.2	228/114
1.5 g (IV)	10	11.4	90/43
1.5 g (IM)	2.5	4.0	250/125
3.0 g (IV)	10	12.3	160/80

The pH of reconstituted solution with solvent supplied with the pack is 3.8 - 5.8. The reconstituted solution is stable for 12 h at 20°C-25° C (68-77°F) and for 48 h at 2°C -8° C (36-46°F).

Intravenous administration: For intravenous infusion, constitute 1.5 g or 3.0 g vial, first with solvent provided and then with an appropriate quantity of one of the compatible IV fluids (See section Compatibility). The resulting solution should be administered over 30-60 minutes.

Intramuscular administration: For IM administration, Supime should be constituted first with solvent provided and then with one of the following diluents; solvent, sterile water for injection, 0.9% Sodium Chloride, 5% Dextrose, 0.5% or 1% Lidocaine Hydrochloride or sterile bacteriostatic water for injection with Parabens or Benzyl Alcohol if needed. IM route of administration is indicated only for mild to moderate, Uncomplicated UTI's due to susceptible pathogens.

Compatibility: Parental drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permits.

Intravenous Cefepime and sulbactam is compatible with the following IV infusion fluids; 0.9% sodium chloride, 5% and 10% dextrose, m/6 sodium lactate, 5% dextrose and 0.9% sodium chloride, lactated ringers and 5% dextrose.

Solutions of cefepime and sulbactam, like those of most beta-lactam antibiotics, should not be added to solutions of ampicillin at a concentration greater than 40 mg/mL and should not be added to metronidazole, vancomycin, gentamycin, tobramycin, netilmicin sulfate or aminophylline

because of potential interaction. However, if concurrent therapy with cefepime and sulbactam is indicated, each of these antibiotics can be administered separately.

SIDE EFFECTS

The following adverse reactions were shown during Phase-III clinical trial of Supime, it was equal to or >1%. i.e phlebitis, pain and/or inflammation, rash. <1% but > 0.1% adverse reactions like colitis, diarrhoea, fever, headache, nausea, oral moniliasis, pruritus, urticaria, vaginitis and vomiting were shown.

Cephalosporin-class adverse reactions: Transient leucopenia, neutropenia, agranulocytosis and thrombocytopenia, Stevens-Johnson syndrome, Erythema multiforme, Toxic epidermal necrolysis, Renal dysfunction, Toxic nephropathy, Aplastic anemia, Hemolytic anemia, Hemorrhage, Hepatic dysfunction including cholestasis and Pancytopenia.

DRUG - DRUG INTERACTIONS

Cefepime-related interactions: Although there are no evidences that cefepime adversely affects renal function at normal therapeutic doses, the usual precautions, such as the monitoring of renal function, should be applied if drugs with nephrotoxic potential (such as aminoglycosides and potent diuretics) are administered with Supime. Nephrotoxicity has been reported following concomitant administration of other cephalosporins with potent diuretics such as furosemide. Renal function should be monitored during concomitant use of loop diuretics or aminoglycosides.

Sulbactam-related interactions: Delayed sulbactam excretion is seen when co-administered with probenecid. There is no information on occurrence of an interaction because of sulbactam addition, which is not observed in beta-lactam antibiotic combinations without sulbactam addition, in trials performed for sulbactam in combination with beta-lactam antibiotics. All interactions reported for sulbactam in combination with mezlocillin, piperacillin, cefotaxime or penicillin G are possible interactions due to the antibiotic component.

CONTRAINDICATIONS

Supime is contraindicated in patients who are hypersensitive to the cefepime, sulbactam or cephalosporins or any of the ingredients of the medicinal product. Before therapy with Supime injection is instituted, careful inquiry should be made to determine whether the patient have had previous immediate hypersensitivity reactions. Exercise caution if this product is to be given to penicillin-sensitive patients because cross-hypersensitivity among beta-lactam antibiotics has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction to Supime occurs, discontinue the drug. Due to its L-arginine content, Supime is

further contraindicated in patients with L-arginine hypersensitivity and acidosis. Caution is therefore advised in cases of hyperkalaemia.

WARNINGS

Use in patients with renal impairment: In patients with creatinine clearance less than or equal to 50 mL/min, adjust the dose of cefepime to compensate for the slower rate of renal elimination. Continued dosage should be determined by degree of renal impairment, severity of infection and susceptibility of the causative organisms.

Neurotoxicity: During PMS of cefepime, serious adverse reactions have been reported including life threatening or fatal occurrences of the following: encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor and coma), myoclonus, seizures and non-convulsive status epilepticus. Most cases occurred in patients with renal impairment who did not receive appropriate dosage adjustment. However, some cases of neurotoxicity occurred in patients receiving a dosage adjustment appropriate for their degree of renal impairment. In the majority of cases, symptoms of neurotoxicity were reversible and resolved after discontinuation of cefepime and/or after haemodialysis. If neurotoxicity associated with Supime therapy occurs, consider discontinuing or making appropriate dosage adjustments in patients with renal impairment.

Clostridium difficile associated diarrhoea: Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including cefepime and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile. Careful medical history is necessary, since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General: Prescribing Supime in the absence of a proven or strongly suspected bacterial infection increases the risk of the development of drug-resistant bacteria.

Many cephalosporins, including cefepime, have been associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy. Positive direct Coombs' tests have been reported during treatment with cefepime. Arginine has been shown to alter glucose metabolism and elevate serum potassium transiently when administered at 33 times the amount provided by the maximum recommended human dose of Supime.

Carcinogenesis, mutagenesis, impairment of fertility: No animal carcinogenicity studies have been conducted with Supime. In chromosomal aberration studies, cefepime was positive for clastogenicity in primary human lymphocytes, but negative in Chinese hamster ovary cells. In other in vitro assays (bacterial and mammalian cell mutation, DNA repair in primary rat hepatocytes and sister chromatid exchange in human lymphocytes), cefepime was negative for genotoxic effects. Moreover, in vivo assessments of cefepime in mice (2 chromosomal aberration and 2 micronucleus studies) were negative for clastogenicity. No untoward effects on fertility were observed in rats when cefepime was administered subcutaneously at doses up to 1000 mg/kg/day hence Supime also is considered safe.

Pregnancy: Safety is not established.

Nursing mothers: Cefepime and Sulbactam is excreted in human breast milk in very low concentrations. Caution should be exercised when administered to a nursing woman.

Labor and delivery: Safety is not established. Treatment should only be given if clearly indicated.

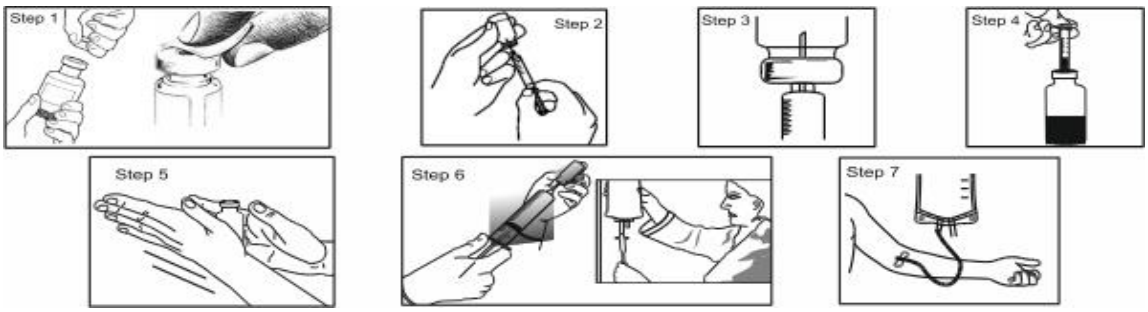
Geriatric use: Clinical efficacy & safety in normal geriatric adults is proven. Serious adverse events have occurred in geriatric patients with renal insufficiency given unadjusted doses of cefepime, including life-threatening or fatal occurrences of the following: encephalopathy, myoclonus and seizures. Risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored.

OVERDOSAGE

Patients who receive an overdose should be carefully observed and given supportive treatment. In the presence of renal insufficiency, hemodialysis not peritoneal dialysis, is recommended to aid in the removal of cefepime from the body. Symptoms of overdose include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor and coma), myoclonus, seizures and neuromuscular excitability.

Instructions for use: The procedures below are provided as general guidelines for the reconstitution and administration of Supime. Agitate the vial gently until the powder dissolves completely. Withdraw all of the dissolved solution from the powder vial into the syringe and then inject either to patient as IM or in an infusion bag. Mix the solution, DO NOT USE if it has particles in it. Administer the solution via intravenous or IM route. Cleanse the injection site with a new alcohol swab prior to administration.

Reconstitution procedure: Reconstitute Supime(Cefepime & Sulbactum for Injection) Along with Solvent provided in pack.



CLINICAL STUDY

Among 340 patients who received Supime identified as resistant to cephalosporins and penicillins, 310 (91.2 %) showed complete clinical cure in terms of total relief and no-disease symptoms, 23 (6.7 %) showed improvement in terms of signs and symptoms, 07 (2.1 %) showed treatment failure (Figure 1). Overall, at screening 340 positive isolates were found in study population which shows 97.9 % (333/340) bacterial eradication on completion of treatment and 2.1 % (07/340) isolates showed failure to eradicate on completion of treatment. (Figure 2).

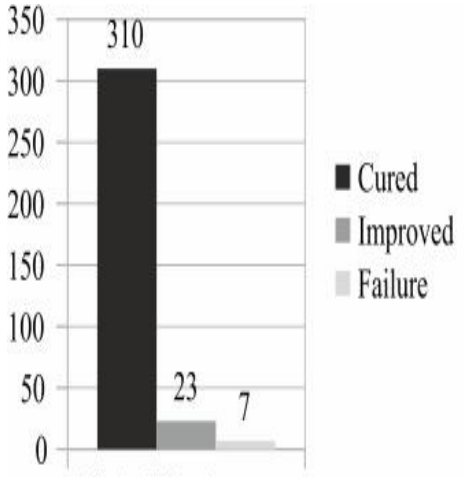


Fig 1: Clinical cure

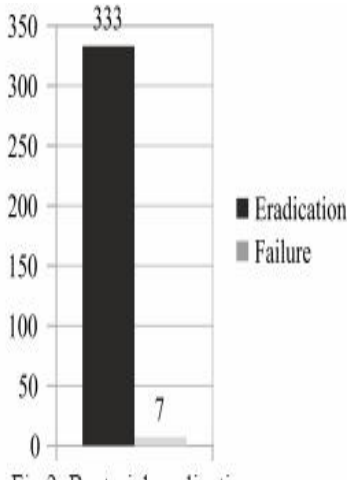


Fig 2: Bacterial eradication

Post marketing surveillance study: During PMS, data of 1500 patients with various bacterial infections (282 LRTI, 880 UTI and 338 Bacterial sepsis) were evaluated for safety and efficacy. Out of 1500 patients, 1485 patients completed the treatment. The reported AEs as per system organ class were as, 3.8 % Dermatology/Skin disorder (like injection site reactions, phlebitis and skin rash), 1.5 % Gastrointestinal disorders (like nausea and vomiting) and 0.5 % nervous system disorder (like headache). In tolerability assessment 43.5 % patients have excellent response, 53.2 % patients have good response, 2.2 % patients have fair response and 1.0 % have not well tolerated response. In efficacy analysis of 1485 patients, 98.1 % showed complete clinical cure in terms of total relief and no-disease symptoms and only 1.9 % showed treatment failure. As per indication, 97.2 % clinical cure in LRTI group, 98.7 % clinical cure in UTI group and 96.9 % clinical cure in Bacterial sepsis

group. Bacteriological eradication was observed in 97.3% of patients in whom bacteria was isolated i.e. 1335/1373.

PHARMACEUTICAL PARTICULARS

STORAGE AND STABILITY: Store at control room temperature below 25°C and protect from light. Do not freeze. Keep out of reach of children. The reconstituted solution is stable for 12 h at 20°C - 25°C (68-77°F) and for 48 h at 2°C-8°C (36-46°F). Shelf life - 24 months without reconstitution when stored at recommended storage conditions.

PACKAGING INFORMATION

Supime is supplied as a sterile dry powder for injection. Each vial of cefepime and sulbactam for injection is filled in flint vials with butyl plug and flip off seal in unit pack and is supplied with solvent for reconstitution. Supime 1.5 g vial with 10 mL of solvent and 3.0 g vial with 20 mL of solvent.

HANDLING DISPOSAL

Parental drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit. Any unused product or waste material should be disposed of in accordance with local requirements.

Research Product of Venus Medicine Research Centre
Patent Under Registration

TM – Trademark applied for

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