1. NAME OF THE MEDICINAL PRODUCT

(PIMCEF INJECTION) Cefepime for Injection USP 1g `

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Combi pack contains:

Each vial contains

Cefepime Hydrochloride USP

Equivalent to Cefepime 1g

(Sterile mixture of Cefepime Hydrochloride and L-Arginine)

Sterile Water for Injection BP 10ml

3. PHARMACEUTICAL FORM

Dry powder for injection; white to yellow powder

4. Clinical particulars

4.1 Therapeutic indications

Cefepime is indicated for the treatment of the severe infections listed below caused by cefepime susceptible pathogens.

In adults and children over 12 years of age and with a body weight of ≥ 40 kg:

- Pneumonia
- Complicated urinary tract infections (including pyelonephritis)
- Complicated intra-abdominal infections
- Peritonitis associated with dialysis in patients on CAPD In adults:
- Acute biliary tract infections

In children aged 2 months up to 12 years and with a body weight of ≤40 kg:

- Pneumonia
- Complicated urinary tract infections
- Bacterial meningitis

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above. Cefepime may be used in the empirical treatment of adults, adolescents and children aged 2 months to 12 years with febrile neutropenia that is suspected to be due to a bacterial infection. In patients at high risk of severe infections (e.g. patients with recent bone marrow transplantation, hypotension at presentation, underlying haematological malignancy, or severe or prolonged neutropenia), antimicrobial monotherapy may be inappropriate. No sufficient data exist to support the efficacy of cefepime monotherapy in such patients. A combination therapy with an aminoglycoside or glycopeptide antibiotic may be advisable, taking into consideration the patient's individual risk profile. Cefepime should be co-administered with other antibacterial

agents whenever the possible range of causative bacteria would not fall within its spectrum of activity Consideration should be given to the official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

After reconstitution cefepime can be administered intravenously as a slow injection over a period of 3 to 5 minutes or as a short infusion over a period of about 30 min. Posology and method of administration are guided by the nature and severity of infection, pathogen susceptibility, renal function, and the patient's overall constitution. Dosage in patients with normal renal function:

Adults and adolescents over 40 kg body weight (approximately over 12 years):

Single doses and dosage interval	Very severe infections: • Complicated intra-abdominal infections • Empirical treatment of patients with febrile neutropenia 2.0 g every 8 hours
Severe infections: · Bacteraemia · Pneumonia · Complicated urinary tract infections (Including pyelonephritis) Acute biliary tract infections 2.0g every 12 hours	

Infants and children (aged from 1 month to 12 years and/or weighing ≤ 40 kg, with normal renal function).

Single doses (mg/kg body weight), dosage interval and treatment duration		
	Severe infections: · Pneumonia · Complicated urinary tract infections (Including pyelonephritis)	Very severe infections: · Bacteraemia · Bacterial meningitis · Empirical treatment of patients with febrile neutropenia
Children from 2 months, body weight ≤ 40 kg:	50 mg/kg every 12 hours More severe infections: 50mg/kg every 8 hours for 10 days	50 mg/kg every 8 hours for 7-10 days
Infants 1 to less than 2 months:	30 mg/kg every 12 hours More severe infections: 30mg/kg every 8 hours for 10days	30 mg/kg every 8 hours for 7-10 days

Experience in infants younger than 2 months is limited. Dosage recommendations of 30 mg/kg every 12 or 8 hours were derived from pharmacokinetic data of children older than 2 months and are considered appropriate for infants from 1 to less than 2 months.

For children weighing > 40 kg dosage recommendations for adults are applicable. For patients older than 12 years with a body weight < 40 kg, dosage recommendations for younger patients with a body weight of < 40 kg are applicable. The maximum recommended daily dose of 2 g every 8 h as for adults should not be exceeded.

Dosage in patients with impaired renal function: In patients with impaired renal function, the dose of cefepime should be adjusted to compensate for the slower rate of renal elimination.

Adults and adolescents (>12 years and body weight over 40 kg): For patients with mild to moderate renal impairment an initial dose of 2.0 g cefepime is recommended.

The following table gives the subsequent maintenance dose:

Creatinine clearance [ml/min]	Recommended maintenance dosage: Single doses and interval of administration	
	Severe infections: · Bacteraemia · Pneumonia · Complicated urinary tract infections (including pyelonephritis) · Acute biliary tract infections	Very severe infections: · Complicated intra-abdominal infections · Empirical treatment of patients with febrile neutropenia
> 50	2 g every 12 h	2 g every 8 h
30-50	2 g every 24 h	2 g every 12 h
11-29	1 g every 24 h	2 g every 24 h
≤ 10	0.5 g every 24 h	1 g every 24 h

Dialysis patients: In patients undergoing haemodialysis, approximately 68% of the total amount of cefepime present in the body at the start of dialysis will be eliminated during a 3 hour dialysis period. Pharmacokinetic modelling indicates that dose reduction is necessary in these patients.

The following dosage is recommended: Loading dose of 1 g on the first day of treatment with cefepime followed by 500 mg per day thereafter except for febrile neutropenia, for which indication the recommended dose is 1 g per day. On days of dialysis, cefepime should be administered after the course of dialysis. If possible, cefepime should be administered at the same time each day.

In patients undergoing continuous ambulatory peritoneal dialysis (CAPD) the following dosage is recommended:

· 1 g cefepime every 48 hours in case of severe infections (bacteraemia, pneumonia, complicated urinary tract infections (including pyelonephritis), acute biliary tract infections)

· 2 g cefepime every 48 hours in case of very severe infections (abdominal infections, peritonitis, empirical treatment of patients with febrile neutropenia) Infants from 1 month and children up to 12 years with a body weight of ≤ 40 kgA dose of 50 mg/kg for patients between 2 months and 12 years (see section 5.2) and a dose of 30 mg/kg for infants aged 1 to 2 months is comparable to a dose of 2 g in adults including the same prolongation of dosing intervals.

4.3 Contraindications

Cefepime is contraindicated in patients who have had previous hypersensitivity reactions to cefepime, to any of the excipients listed in section 6.1., to any other cephalosporin or to any other beta-lactam antibiotics agent (e.g. penicillins, monobactams and carbapenems). Due to its L-arginine content, this product is further contraindicated in patients with L-arginine hypersensitivity and acidosis. Caution is therefore advised in cases of hyperkalemia.

4.4 Special warnings and precautions for use

Hypersensitivity reactions: As with all beta-lactam antibacterial agents, severe and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment

with cefepime must be discontinued immediately and adequate emergency measures must be initiated. Before therapy with cefepime is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefepime, beta-lactams or other medicinal products. In 10 % of the cases there is cross-reactivity between hypersensitivity to penicillin and cephalosporins. Cefepime should be administered with caution to patients with a history of asthma or allergic diathesis. The patient must be carefully monitored during the first administration. If an allergic reaction occurs, treatment must be discontinued immediately. Serious hypersensitivity reactions may require epinephrine and other supportive therapy.

Antibacterial activity of cefepime: Due to the relatively limited spectrum of antibacterial activity of cefepime it is not suitable for treatment of some types of infections unless the pathogen is already documented and known to be susceptible or there is a very high suspicion that the most likely pathogen(s) would be suitable for treatment with cefepime.

Renal impairment: In patients with impaired renal function (creatinine clearance ≤ 50 ml/min) or other conditions that may compromise renal function, the dosage of cefepime should be adjusted to compensate for the slower rate of renal elimination. Because high and prolonged serum antibiotic concentrations can occur from usual dosages in patients with renal insufficiency or other conditions that may compromise renal function, the maintenance dosage should be reduced when cefepime is administered to such patients. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organisms. During post-marketing surveillance, the following serious adverse events have been reported: reversible encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures (including non-convulsive status epilepticus), and/or renal failure (see section 4.8). Most cases occurred in patients with renal impairment who received doses of cefepime that exceeded recommendations. In general, symptoms of neurotoxicity resolved after discontinuation of cefepime and/or after haemodialysis, however, some cases included a fatal outcome.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Positive Coombs test without haemolysis was detected in patients receiving cefepime two times daily (see section 4.8). The result of glucose determination from urine may be false positive therefore glucose oxidase method is suggested. Concomitant treatment with bacteriostatic antibiotics may interfere with the action of beta lactam antibiotics.

4.6 Pregnancy and Lactation

Pregnancy

Reproductive studies in mice, rats, and rabbits showed no evidence of fetal damage, however there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Breastfeeding

Cefepime is excreted in human breast milk in very low concentrations. Caution should be used when cefepime is administered to a nursing woman, then the infant should be monitored closely.

Fertility: No impairment of fertility has been seen in rats.

4.7 Effects on ability to drive and use machines

The effects of medicinal product on ability to drive and use machines have not been studied. However, possible adverse reactions like altered state of consciousness, dizziness, confusional state or hallucinations may alter the ability to drive and use machines.

4.8 Undesirable effects

The most reported adverse drug reactions (ADRs) are diarrhoea, nausea, and vomiting. The ADRs derived from clinical studies and post-marketing surveillance with Co-amoxiclav, sorted by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the occurrence of undesirable effects.

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)

Not known (cannot be estimated from the available data)

Infections and infestations	
Mucocutaneous candidosis	Common
Overgrowth of non-susceptible organisms	Not known
Blood and lymphatic system disorders	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time	Not known
Immune system disorders	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Hypersensitivity vasculitis	Not known
Nervous system disorders	
Dizziness	Uncommon

Headache	Uncommon

4.9 Overdose

In case of severe overdosage, especially in patients with compromised renal function, hemodialysis will aid in the removal of cefepime from the body; peritoneal dialysis is of no value. Accidental overdosing has occurred when large doses were given to patients with impaired renal function (see sections 4.2 - Posology and administration and 4.4 – Special warnings and precautions for use). Symptoms of overdose include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and seizures.

5 PHARMACOLOGICAL PROPERTIES

5.2 Pharmacodynamics properties

Pharmacotherapeutic Group: Fourth generation cephalosporins

ATC code: J01DE01

Mechanism of Action

The mechanism of action of cefepime is based on inhibition of bacterial cell wall synthesis (in the growth phase), due to inhibition of penicillin-binding proteins (PBPs) e.g. transpeptidases. This results in a bactericidal action.

PD/PK relationship Efficacy is largely dependent on the length of time during which drug levels exceed the minimal inhibitory concentration (MIC) of the pathogen concerned. Mechanism of resistance Cefepime has a low affinity for chromosomally-encoded beta-lactamases and is highly resistant to hydrolysis by most beta-lactamases. Bacterial resistance to cefepime may be due to one or more of the following mechanisms: · reduced affinity of penicillin-binding proteins for cefepime, · production of β-lactamases which are able to hydrolyse cefepime efficiently (e.g, several of the extended-spectrum and chromosomally mediated β-lactamases), · outer membrane impermeability, which restricts access of cefepime to penicillin binding proteins in gram-negative organisms, efflux pumps for active substances.

There is partial or complete cross resistance between cefepime and other cephalosporins and penicillins. Cefepime testing is performed using the standard dilution series

The prevalence of 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.

Commonly susceptible species

Aerobic Gram-positive micro-organisms

Enterococcus faecalis

Gardnerella vaginalis

Staphylococcus aureus (methicillin-susceptible)£

Streptococcus agalactiae

Streptococcus pneumoniae1

Streptococcus pyogenes and other beta-haemolytic streptococci
Streptococcus viridans group
Aerobic Gram-negative micro-organisms
Actinobacillus actinomycetemcomitans
Capnocytophaga spp.

Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms
Enterococcus faecium $
Aerobic Gram-negative micro-organisms
Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae
Proteus mirabilis
Proteus vulgaris
Inherently resistant organisms
Aerobic Gram-negative micro-organisms
Acinetobacter sp.
Citrobacter freundii
Enterobacter sp.
Legionella pneumophila
Morganella morganii

5.3 Pharmacokinetic properties

The pharmacokinetic properties of cefepime are linear within the range of 250 mg to 2 g i.v.; they do not differ regarding duration of treatment.

Absorption
After i.v. administration of 2 g over 30 minutes to healthy volunteers, peak plasma concentrations (Cmax) were 126 - 193 µg/ml.

Distribution
Cefepime is well distributed in bodily fluids and tissues. Within the range of 250 mg to 2 g, the relative tissue distribution of cefepime does not vary in relation to the administered dose. The mean steady-state volume of distribution is 18 l. There is no evidence of any accumulation in healthy subjects given doses of up to 2 g i.v.at 8-hourly intervals over a 9-day period. Serum protein binding of cefepime is < 19% and is not dependent on serum concentrations. The mean elimination half-life is approximately 2 hours.

Biotransformation
Cefepime is metabolised to a minor extent. The primary urinary metabolite is N-methylpyrrolidine oxide, a tertiary amine, accounting for only around 7% of the dose.

Elimination

Mean total body clearance is 120 ml/min. The mean renal clearance of cefepime is 110 ml/min; this shows that cefepime is almost exclusively eliminated via renal mechanisms, mainly by glomerular filtration. Urine recovery of unchanged cefepime is approximately 85% of the dose, leading to high urinary concentrations of cefepime. Following i.v. administration of 500 mg cefepime, cefepime was no longer detectable after 12 hours in plasma and after 16 hours in urine.

5.4 Preclinical safety data

Although no long-term animal studies have been performed to evaluate carcinogenic potential, in vivo and in vitro testing has shown that cefepime is not genotoxic. Studies in animals have shown that daily doses of up to 10 times the recommended dose in humans do not have any direct or indirect harmful effects on reproduction, embryonal/foetal development, duration of gestation or peri-/postnatal development.

6 PHARMACEUTICAL PARTICULARS

6.1 None

6.2 Incompatibilities

Solutions of Cefepim MIP must not be mixed with the following antibiotics: metronidazole, vancomycin, gentamicin, tobramycin sulphate and netilmicin sulphate, because physical or chemical incompatibilities may arise. Should concomitant therapy be indicated, such agents must be administered separately. All parenteral products should be visually inspected for particles prior to administration.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a cool and dry place below 30°C, protect from light

6.5 Nature and contents of container <and special equipment for use, administration, or implantation>

20 ml USP type I Glass vial closed with Bromo Butyl Rubber Stopper and Sealed with F/O Aluminium seal.

6.6 Special precautions for disposal <and other handling>

Preparation of the solution for i.v. injection The vial contents are dissolved in 10 ml solvent as indicated in the table below. The prepared solution is injected slowly over a 3 to 5-minute period - either directly into a vein or directly into the cannula of an infusion system whilst the patient is receiving an infusion with a compatible i.v. solution.

Preparation of the solution for i.v. infusion

For intravenous infusion, reconstitute the 1 g or 2 g cefepime solution, as noted above for direct intravenous administration; and add the required quantity of the resulting solution to a container with one of the compatible i.v. fluids (recommended final volume: about 40-50 ml). The prepared solution should be administered over a period of approximately 30 minutes.

Compatibility with intravenous liquids

The following solvents are suitable for preparation of the solution:

- Water for injections
- Glucose solution 50 mg/ml (5%)
- Sodium chloride solution 9 mg/ml (0.9%).

The reconstitution/dilution is to be made under aseptic conditions. Add the recommended volume of reconstitution solution and shake gently until the contents of the vial have dissolved completely. For single use only. Any remaining solution should be discarded. Any unused product or waste material should be disposed of in accordance with local requirements.

Inspect the vial before use. It must only be used if the solution is free from particles. Use only clear solutions. Like other cephalosporins, cefepime solutions can develop a yellow to amber colour, depending on storage conditions.

7 APPLICANT

Evans Baroque Nigeria Limited
Km 32, Lagos – Badagry Expressway,
Agbara Industrial Estate, Agbara,
Ogun State, Nigeria
08033304149

info@evansbaroque.com

MANUFACTURER

Inject Care Parenterals Pvt. Ltd
Plot no. 130, Silvassa Road,
G.ID. C. Vapi-396195, Gujurat,
India
+91-6359299966, 8511149413

contact@injectcare.com