MODULE 1- ADMINISTRATIVE PARTICULARS OF THE PRODUCT

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1.3.1.1. Name of the medicinal product:

1.3.1.1.1 (Invented) name of the medicinal product:

- **Generic Name/INN Name:** Cefuroxime for injection USP
- **Brand Name :** CEFUJET INJECTION

1.3.1.1.2 Strength:

Each vial contains:
Cefuroxime sodium USP
Eq. to Cefuroxime 750 mg

1.3.1.1.3 Pharmaceutical form:

Powder for injection

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1.3.1.2. Qualitative and Quantitative Composition:

Sr. No.	Ingredients.	Spec.	Std. Qty mg / Vial	Function
1.	Sterile Cefuroxime sodium eq. to Cefuroxime	USP	848 mg*	Antibiotic

Calculation:

Note:

Calculation:

Weight of cefuroxime sodium USP
Assay on anhydrous basis: 90.85 (It contains the equivalent of NLT 855 µg & NMT 1000 µg of Cefuroxime (C16H16N4O8S), water: 2.65 (Not more than 3.5%)
MRN No.: BPBR10402 A. R. No.: QBPBR10402

$$= \frac{750 \times 100 \times 100}{\text{Potency of Cefuroxime Sodium on anhydrous basis} \times (100 - \% \text{ of water})}$$

$$= \frac{0.750 \times 100 \times 100}{90.85 \times (100-2.65)}$$

= 848 mg/vial

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1.3.1.3. Pharmaceutical form:

- **Dosage Form :** Powder for injection (Injectable)
- **Visual & Physical characteristics of the product:** An off-white powder filled in an intactly sealed clear glass vials.

1.3.1.4. Clinical particulars:

1.3.1.4.1 Therapeutic indications:

Cefuroxime is a bactericidal cephalosporin antibiotic which is resistant to most β-lactamases and is active against a wide range of Gram-positive and Gram-negative organisms. It is indicated for the treatment of infections before the infecting organism has been identified or when caused by sensitive bacteria.

Respiratory tract infections for example, acute and chronic bronchitis, infected bronchiectasis, bacterial pneumonia, lung abscess and post-operative chest infections.

Ear, nose and throat infections for example, sinusitis, tonsillitis, pharyngitis and otitis media.

Urinary tract infections for example, acute and chronic pyelonephritis, cystitis and asymptomatic bacteriuria.

Soft-tissue infections for example, cellulitis, erysipelas and wound infections.

Bone and joint infections for example, osteomyelitis and septic arthritis.

Obstetric and gynaecological infections, pelvic inflammatory diseases.

Gonorrhoea particularly when penicillin is unsuitable.

Other infections including septicaemia, meningitis and peritonitis.

Prophylaxis against infection in abdominal, pelvic, orthopaedic, cardiac, pulmonary, oesophageal and vascular surgery where there is increased risk from infection.

Cefuroxime Sodium for Injection will be effective alone, but when appropriate it may be used in combination with an aminoglycoside antibiotic, or in conjunction with

metronidazole (orally or by suppository or injection), especially for prophylaxis in colonic or gynaecological surgery.

1.3.1.4.2 Posology and method of administration:

Dosage and Administration:

Cefuroxime Sodium for Injection is for intravenous and/or intramuscular administration.

Adults and children ≥ 40kg

Indication	**Dosage**
Community acquired pneumonia and acute exacerbations of chronic bronchitis	750 mg every 8 hours (intravenously or intramuscularly)
Soft-tissue infections: cellulitis, erysipelas and wound infections	
Intra-abdominal infections	
Complicated urinary tract infections, including pyelonephritis	1.5g every 8 hours (intravenously or intramuscularly)
Severe infections	750 mg every 6 hours (intravenously) 1.5 g every 8 hours (intravenously)
Surgical prophylaxis for gastrointestinal, gynaecological (including caesarean section) and orthopaedic operations	1.5 g with the induction of anaesthesia. This may be supplemented with two 750 mg doses (intramuscularly) after 8 hours and 16 hours.
Surgical prophylaxis for cardiovascular and oesophageal operations	1.5 g with induction of anaesthesia followed by 750 mg (intramuscularly) every 8 hours for a further 24 hours.

Children < 40kg

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	Infants and toddlers > 3 weeks and children < 40 kg	**Infants (birth to 3 weeks)**
Community acquired pneumonia	30 to 100 mg/kg/day (intravenously) given as 3 or 4 divided doses; a dose of 60 mg/kg/day is appropriate for most infections	30 to 100 mg/kg/day (intravenously) given as 2 or 3 divided doses (see section 5.2)
Complicated urinary tract infections, including pyelonephritis		
Soft-tissue infections: cellulitis, erysipelas and wound infections		
Intra-abdominal infections		

Renal impairment

Cefuroxime is primarily excreted by the kidneys. Therefore, as with all such antibiotics, in patients with markedly impaired renal function it is recommended that the dosage of cefuroxime should be reduced to compensate for its slower excretion.

Recommended doses for Cefuroxime in renal impairment.

Creatinine clearance	**$T_{1/2}$ (hrs)**	**Dose mg**
> 20 mL/min/1.73 m^2	1.7–2.6	It is not necessary to reduce the standard dose (750 mg to 1.5 g three times daily).
10-20 mL/min/1.73 m^2	4.3–6.5	750 mg twice daily
< 10 mL/min/1.73 m^2	14.8–22.3	750 mg once daily
Patients on haemodialysis	3.75	A further 750 mg dose should be given intravenously or intramuscularly at the end of each dialysis; in addition to

		parenteral use, cefuroxime sodium can be incorporated into the peritoneal dialysis fluid (usually 250 mg for every 2 litres of dialysis fluid).
Patients in renal failure on continuous arteriovenous haemodialysis (CAVH) or high-flux haemofiltration (HF) in intensive therapy units	7.9–12.6 (CAVH) 1.6 (HF)	750 mg twice daily; for low-flux haemofiltration follow the dosage recommended under impaired renal function.

Hepatic impairment

Cefuroxime is primarily eliminated by the kidney. In patients with hepatic dysfunction this is not expected to affect the pharmacokinetics of cefuroxime.

Method of administration

Cefuroxime should be administered by intravenous injection over a period of 3 to 5 minutes directly into a vein or via a drip tube or infusion over 30 to 60 minutes, or by deep intramuscular injection. For instructions on reconstitution of the medicinal product before administration.

Instruction for constitution

Addition volumes and solution concentrations, which may be useful when fractional doses are required			
Vial size	Displacement (ml)	Amount of water to be added (ml)	Approximate cefuroxime concentration (mg/mL)
750 mg powder for solution for injection			

750mg	intramuscular intravenous bolus	0.6ml	3 mL 6 mL	216 116

* Reconstituted solution to be added to 35ml of compatible infusion fluid

1.3.1.4.3 Contraindications:

Hypersensitivity to Cefuroxime or any of the cephalosporin antibiotics. Previous immediate and/or severe hypersensitivity reaction to penicillin or to any other type of beta-lactam drug.

1.3.1.4.4 Special warnings and precautions for use:

Hypersensitivity reactions

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with cefuroxime must be discontinued immediately and adequate emergency measures must be initiated.

Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to cefuroxime, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if cefuroxime is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

Concurrent treatment with potent diuretics or aminoglycosides

Cephalosporin antibiotics at high dosage should be given with caution to patients receiving concurrent treatment with potent diuretics such as furosemide or aminoglycosides. Renal impairment has been reported during use of these combinations. Renal function should be monitored in the elderly and those with known pre-existing renal impairment.

Overgrowth of non-susceptible microorganisms

Use of cefuroxime may result in the overgrowth of *Candida.* Prolonged use may also result in the overgrowth of other non-susceptible microorganisms (e.g. *enterococci* and *Clostridium difficile*), which may require interruption of treatment.

Antibacterial agent–associated pseudomembranous colitis has been reported with use of cefuroxime and may range in severity from mild to life threatening. This diagnosis should be considered in patients with diarrhoea during or subsequent to the administration of cefuroxime. Discontinuation of therapy with cefuroxime and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Intra-abdominal infections

Due to its spectrum of activity, cefuroxime is not suitable for the treatment of infections caused by Gram-negative non-fermenting bacteria.

Interference with diagnostic tests

The development of a positive Coomb's Test associated with the use of cefuroxime may interfere with cross matching of blood.

Slight interference with copper reduction methods (Benedict's, Fehling's, Clinitest) may be observed. However, this should not lead to false-positive results, as may be experienced with some other cephalosporins.

As a false negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase methods are used to determine blood/plasma glucose levels in patients receiving cefuroxime sodium.

Important information about excipients

Cefuroxime powder for solution for injection and infusion contains sodium. This should be considered for patients who are on a controlled sodium diet.

1.3.1.4.5 Interaction with other medicinal products and other forms of interaction:

Cefuroxime may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

Cefuroxime is excreted by glomerular filtration and tubular secretion. Concomitant use of probenicid is not recommended. Concurrent administration of probenecid prolongs the excretion of the antibiotic and produces an elevated peak serum level.

Potential nephrotoxic drugs and loop diuretics

High-dosage treatments with cephalosporins should be carried out with caution on patients who are taking strong-acting diuretics (such as furosemide) or potential nephrotoxic preparations (such as aminoglycoside antibiotics), since impairment of renal function through such combinations cannot be ruled out.

Other Interactions

Determination of blood/plasma glucose levels: As a false negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase methods are used to determine blood/plasma glucose levels in patients receiving cefuroxime sodium.

Concomitant use with oral anticoagulants may give rise to increased international normalised ratio (INR).

1.3.1.4.6 Pregnancy and lactation:

Pregnancy

There are limited amounts of data from the use of cefuroxime in pregnant women. Studies in animals have shown no reproductive toxicity. Cefuroxime should be prescribed to pregnant women only if the benefit outweighs the risk.

Cefuroxime has been shown to cross the placenta and attain therapeutic levels in amniotic fluid and cord blood after intramuscular or intravenous dose to the mother.

Breastfeeding

Cefuroxime is excreted in human milk in small quantities. Adverse reactions at therapeutic doses are not expected, although a risk of diarrhoea and fungus infection of the mucous membranes cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from cefuroxime therapy taking into

account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effects of cefuroxime sodium on fertility in humans. Reproductive studies in animals have shown no effects on fertility.

1.3.1.4.7 Effects on ability to drive and use machines

No studies on the effects of cefuroxime on the ability to drive and use machines have been performed. However, based on known adverse reactions, cefuroxime is unlikely to have an effect on the ability to drive and use machines.

1.3.1.4.8 Undesirable effects:

Adverse reactions to cefuroxime have occurred relatively infrequently and have been generally mild and transient in nature.

There have been rare reports of hypersensitivity reactions including skin rashes, urticaria, pruritus, interstitial nephritis, drug fever and very rarely anaphylaxis.

As with other cephalosporins, there have been rare reports of erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis (exanthematic necrolysis).

As with other antibiotics, prolonged use may result in the overgrowth of non-susceptible organisms, e.g. *Candida*.

Gastro-intestinal disturbance, including, very rarely, symptoms of pseudomembranous colitis may occur during or after treatment.

The principal changes in haematological parameters seen in some patients have been decreased haemoglobin concentration and of eosinophilia, leukopenia, neutropenia and thrombocytopenia.

Cephalosporins as a class tend to be absorbed onto the surface of red cells membranes and react with antibodies directed against the drug to produce a positive Coombs' test (which can interfere with cross-matching of blood) and very rarely haemolitic anaemia.

Although there are sometimes transient rises in serum liver enzymes or serum bilirubin, particularly in patients with pre-existing liver disease, there is no evidence of harm to the liver.

Elevations in serum creatinine and/or blood urea nitrogen and a decreased creatinine clearance have been observed (see Warnings and Precautions).

Transient pain may be experienced at the site of intramuscular injection. This is more likely to occur with higher doses. However it is unlikely to be a cause for discontinuation or treatment.

Occasionally, thrombophlebitis may follow intravenous injection.

1.3.1.4.9 Overdose

Overdose can lead to neurological sequel including encephalopathy, convulsions and coma. Symptoms of overdose can occur if the dose is not reduced appropriately in patients with renal impairment.
Serum levels of cefuroxime can be reduced by haemodialysis or peritoneal dialysis.

1.3.1.5. Pharmacological properties:

1.3.1.5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: cephalosporin antibiotic for parenteral administration

ATC classification: J01DC02

Mode of action

Cefuroxime is a semisynthetic derivative of cephalosporanic acid. Cefuroxime exerts antibacterial activity by inhibition of bacterial cell wall synthesis in susceptible species. Cefuroxime has good stability to several bacterial beta-lactamase enzymes and, consequently, is active against many penicillin-resistant or ampicillin and amoxicillin-resistant strains of susceptible species.

PK/PD relationship:

Cefuroxime binds to cell receptors, called penicillin-binding proteins. After a β-lactam antibiotic has bound to these receptors, the transpeptidation reaction is inhibited and peptidoglycan synthesis is blocked. This results in bacterial lysis.

Mechanisms of Resistance to Cefuroxime:

Known mechanisms of resistance in targeted pathogens are the following:

• Production of β-lactamases which are able to hydrolyse cefuroxime efficiently (e.g. several of the extended-spectrum and chromosomally-mediated β-lactamases).

• Reduced affinity of penicillin-binding proteins for cefuroxime (e.g. penicillin-resistant *Streptococcus pneumoniae*).

• Cell wall impermeability.

• Efflux pumps.

The following table gives only an approximate guidance on probabilities whether microorganisms will be susceptible to cefuroxime or not.

Category	Range of Resistance (Europe)
Susceptible	
Aerobic Gram positive	
Staphylococcus epidermidis (methicillin-susceptible strains)	0-46%
Aerobic Gram negative	
Escherichia coli	2-17%
Haemophilus influenzae	0-29%
Klebsiella spp.	6-21%
Proteus mirabilis	0-17%
Providencia spp., including *Providencia rettgeri*	0-75%
Intermediately susceptible	
Aerobic Gram negative	
Citrobacter	21-52%
Enterobacter spp.	36-83%
Insusceptible	

Aerobic Gram negative	
Morganella morganii	70-94%
Proteus vulgaris	75-100%

No resistance data are available for the following organisms

Susceptible

Aerobic Gram positive

Staphylococcus aureus (methicillin-susceptible strains), *Streptococcus pneumoniae*, *Streptococcus pyogenes*,*Streptococcus viridans*.

Aerobic Gram negative

Moraxella catarrhalis, Neisseria spp. *Providencia rettgeri* only.

Anaerobes

Clostridium perfringens

Intermediately Susceptible

Aerobic Gram positive

Bordetella pertussis

Anaerobes

Bacteroides fragilis

Insusceptible

Aerobic Gram positive

Enterococcus faecalis, Staphylococcus aureus (methicillin-resistant strains), *Staphylococcus epidermidis* (methicillin-resistant strains)

Aerobic Gram negative

Acinetobacter spp., Campylobacter spp., Legionella spp., Pseudomonas spp.

Serratia spp.

Anaerobes

Clostridium difficile

Other Information

Cross-Reactivity Between Cefuroxime and Other Antibiotics

Cross-resistance between cefuroxime and several other β-lactam antibiotics, including amoxicillin, methicillin, penicillin and ampicillin and some cephalosporins can occur.

Amoxicillin-sensitive *Haemophilus influenzae* are more likely to be susceptible to cefuroxime than amoxicillin-resistant*Haemophilus influenzae*. Similarly, methicillin-sensitive *Staphylococcus aureus* and *Staphylococcus epidermidis* are usually cefuroxime-susceptible, while methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* are resistant to cefuroxime.

Resistance of *Staphylococcus aureus* and *Staphylococcus pneumoniae* to penicillin can result in an increase in the cefuroxime MIC_{50} and MIC_{90} values for these organisms. In addition, resistance of *Escherichia coli* and *Haemophilus influenzae* to ampicillin may result in an increase of the cefuroxime MIC_{50} values for these organisms

1.3.1.5.2 Pharmacokinetic properties

Absorption

After intramuscular (IM) injection of cefuroxime to normal volunteers, the mean peak serum concentrations ranged from 27 to 35 µg/mL for a 750 mg dose and from 33 to 40 µg/mL for a 1000 mg dose, and were achieved within 30 to 60 minutes after administration. Following intravenous (IV) doses of 750 and 1500 mg, serum concentrations were approximately 50 and 100 µg/mL, respectively, at 15 minutes.

AUC and C_{max} appear to increase linearly with increase in dose over the single dose range of 250 to 1000 mg following IM and IV administration. There was no evidence of accumulation of cefuroxime in the serum from normal volunteers following repeat intravenous administration of 1500 mg doses every 8 hours.

Distribution

Protein binding has been stated as 33 to 50%, depending on the methodology used. The average volume of distribution ranges from 9.3 to 15.8 L/1.73 m^2 following IM or IV

administration over the dosage range of 250 to 1000 mg. Concentrations of cefuroxime in excess of the minimum inhibitory levels for common pathogens can be achieved in the tonsilla, sinus tissues, bronchial mucosa, bone, pleural fluid, joint fluid, synovial fluid, interstitial fluid, bile, sputum and aqueous humour. Cefuroxime passes the blood-brain barrier when the meninges are inflamed.

Biotransformation

Cefuroxime is not metabolised.

Elimination

Cefuroxime is excreted unchanged by glomerular filtration and renal tubular secretion. The serum half-life after either intramuscular or intravenous injection is approximately 70 minutes. There is an almost complete recovery (85 to 90%) of unchanged cefuroxime in urine within 24 hours of administration. The majority of the cefuroxime is excreted within the first 6 hours. The average renal clearance ranges from 114 to 170 mL/min/1.73 m^2 following IM or IV administration over the dosage range of 250 to 1000 mg.

Special patient populations

Gender

No differences in the pharmacokinetics of cefuroxime were observed between males and females following a single IV bolus injection of 1000 mg of cefuroxime as the sodium salt.

Elderly

Following IM or IV administration, the absorption, distribution and excretion of cefuroxime in elderly patients are similar to younger patients with equivalent renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in cefuroxime dose selection, and it may be useful to monitor renal function.

Paediatrics

The serum half-life of cefuroxime has been shown to be substantially prolonged in neonates according to gestational age. However, in older infants (aged >3 weeks) and in children, the serum half-life of 60 to 90 minutes is similar to that observed in adults.

Renal impairment

Cefuroxime is primarily excreted by the kidneys. As with all such antibiotics, in patients with markedly impaired renal function (i.e. $C1_{cr}$<20 mL/minute) it is recommended that the dosage of cefuroxime should be reduced to compensate for its slower excretion . Cefuroxime is effectively removed by haemodialysis and peritoneal dialysis.

Hepatic impairment

Since cefuroxime is primarily eliminated by the kidney, hepatic dysfunction is not expected to have an effect on the pharmacokinetics of cefuroxime.

PK/PD relationship

For cephalosporins, the most important pharmacokinetic-pharmacodynamic index correlating with *in vivo* efficacy has been shown to be the percentage of the dosing interval (%T) that the unbound concentration remains above the minimum inhibitory concentration (MIC) of cefuroxime for individual target species (i.e. %T>MIC).

1.3.1.5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development. No carcinogenicity studies have been performed; however, there is no evidence to suggest carcinogenic potential.

Gamma glutamyl transpeptidase activity in rat urine is inhibited by various cephalosporins, however the level of inhibition is less with cefuroxime. This may have significance in the interference in clinical laboratory tests in humans.

MODULE 1- ADMINISTRATIVE PARTICULARS OF THE PRODUCT

1.3.1.6. Pharmaceutical particulars:

1.3.1.6.1 List of Excipients:

None

1.3.1.6.2 Incompatibilities:

Not applicable

1.3.1.6.3 Shelf life:

24 months

1.3.1.6.4 Special precautions for storage:

Store below 30°C in dry place. Protect from light.

1.3.1.6.5 Nature and contents of container:

Cefuroxime for injection pack in 10 ml Clear glass vials (Type – III), Pack in single monocarton along with WFI and Package information insert.

1.3.1.6.6 Special precautions for disposal:

No special requirement.

MODULE 1- ADMINISTRATIVE PARTICULARS OF THE PRODUCT

1.3.1.7. Registrant:

BHARAT PARENTERALS LTD.

Name : **Bharat Parenterals Ltd.**
Address : 144 & 146, Jarod Samlaya Road,
Vill. Haripura, Ta. Savli,
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INDIA.
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E-mail : bplbrd@yahoo.com, info@bplindia.in, bplbrd@bplindia.in.

1.3.1.8. Manufacturer:

BHARAT PARENTERALS LTD.

Name : **Bharat Parenterals Ltd.**
Address : 144 & 146, Jarod Samlaya Road,
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1.3.1.9. Date of revision of the text:

1.3.1.10. Instructions for Preparation of Radiopharmaceuticals (If Applicable):

Not Applicable