SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AFROXIM 750 for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:

Cefuroxime Sodium USP (Sterile) equivalent to Cefuroxime 750 mg

The product is a sterile dry powder for injection and does not contain any added excipients.

3. PHARMACEUTICAL FORM

Powder for solution for injection/infusion.

A white to faintly yellow crystalline powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cefuroxime is indicated for the treatment of the infections listed below in adults and children, including neonates (from birth):

- Community acquired pneumonia
- Acute exacerbations of chronic bronchitis
- Complicated urinary tract infections, including pyelonephritis
- Soft-tissue infections: cellulitis, erysipelas and wound infections
- Intra-abdominal infections
- Prophylaxis against infection in gastrointestinal (including oesophageal), orthopaedic, cardiovascular and gynaecological surgery (including caesarean section)

In the treatment and prevention of infections in which it is very likely that anaerobic organisms will be encountered, cefuroxime should be administered together with additional appropriate antibacterial agents.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and Method of Administration

Table 1. Adults and children ≥ 40 kg

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	1.5 g every 8 hours (intravenously or intramuscularly)
Severe infections	750 mg every 6 hours (intravenously) or 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.

Table 2. Children < 40 kg

Indication	Infants and toddlers > 3 weeks and children < 40 kg	Infants (birth to 3 weeks)
Community acquired pneumonia; Complicated urinary tract infections, including pyelonephritis; Soft-tissue infections: cellulitis, erysipelas and wound infections; Intra-abdominal infections	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)

Renal impairment

Cefuroxime is primarily excreted by the kidneys. 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.

Table 3. Recommended doses of Cefuroxime in renal impairment

Creatinine clearance	T½ (hrs)	Dose
> 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.

4.3 Contraindications

- Patients with known hypersensitivity to cephalosporin antibiotics.
- History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (penicillins, monobactams and carbapenems).

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 (see section 4.2).

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 the 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 Coombs' 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 be 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.

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 probenecid is not recommended, as it prolongs the excretion of the antibiotic and produces an elevated peak serum level.

Potential nephrotoxic drugs and loop diuretics

High-dosage treatment with cephalosporins should be carried out with caution in patients who are taking strong-acting diuretics (such as furosemide) or potentially 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. Concomitant use with oral anticoagulants may give rise to an increased international normalised ratio (INR).

4.6 Fertility, 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 (see section 5.3). 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.

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.

4.8 Adverse Drug Reactions

The most common adverse reactions are neutropenia, eosinophilia, transient rise in liver enzymes or bilirubin, particularly in patients with pre-existing liver disease, but there is no evidence of harm to the liver and injection site reactions.The frequency categories assigned to the adverse reactions below are estimates, as for most reactions suitable data for calculating incidence are not available. In addition the incidence of adverse reactions associated with cefuroxime sodium may vary according to the indication.

Data from clinical trials were used to determine the frequency of very common to rare adverse reactions. The frequencies assigned to all other adverse reactions (i.e. those occurring at <1/10,000) were mainly determined using post-marketing data, and refer to a reporting rate rather than a true frequency.

Treatment related adverse reactions, all grades, are listed below by MedDRA body system organ class, frequency and grade of severity. The following convention has been utilised for the classification of frequency: very common ≥ 1/10; common ≥ 1/100 to < 1/10, uncommon ≥ 1/1,000 to < 1/100; rare ≥ 1/10,000 to < 1/1,000; very rare < 1/10,000 and not known (cannot be estimated from the available data).

System Organ Class	Common	Uncommon	Not Known
Infections and infestations	-	-	Candida overgrowth, overgrowth of

System Organ Class	Common	Uncommon	Not Known
			Clostridium difficile
Blood and lymphatic system disorders	Neutropenia, eosinophilia, decreased haemoglobin concentration	Leukopenia, positive Coombs' test	Thrombocytopenia, haemolytic anaemia
Immune system disorders	-	-	Drug fever, interstitial nephritis, anaphylaxis, cutaneous vasculitis
Gastrointestinal disorders	-	Gastrointestinal disturbance	Pseudomembranous colitis
Hepatobiliary disorders	Transient rise in liver enzymes	Transient rise in bilirubin	-
Skin and subcutaneous tissue disorders	-	Skin rash, urticaria and pruritus	Erythema multiforme, toxic epidermal necrolysis and Stevens-Johnson syndrome, angioneurotic oedema
Renal and urinary disorders	-	-	Elevations in serum creatinine, elevations in blood urea nitrogen and decreased creatinine clearance
General disorders and administration site conditions	Injection site reactions which may include pain and thrombophlebitis	-	-

Description of selected adverse reactions

Cephalosporins as a class tend to be absorbed onto the surface of red cell 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, haemolytic anaemia.

Transient rises in serum liver enzymes or bilirubin have been observed, which are usually reversible. Pain at the intramuscular injection site is more likely at higher doses; however, it is unlikely to be a cause for discontinuation of treatment.

Paediatric population

The safety profile for cefuroxime sodium in children is consistent with the profile in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

Overdose can lead to neurological sequelae including encephalopathy, convulsions and coma. Symptoms of overdose can

occur if the dose is not reduced appropriately in patients with renal impairment (see sections 4.2 and 4.4).

Serum levels of cefuroxime can be reduced by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antibacterials for systemic use, second-generation cephalosporins.

ATC code: Cefuroxime Sodium — J01DC02

Mode of action

Cefuroxime inhibits bacterial cell wall synthesis following attachment to penicillin-binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

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, 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 Cmax appear to increase linearly with increasing 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 of normal volunteers following repeat intravenous administration of 1500 mg doses every 8 hours.

Distribution

Protein binding has been reported 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 tonsils, sinus tissues, bronchial mucosa, bone, pleural fluid, joint fluid, synovial fluid, interstitial fluid, bile, sputum and aqueous humour. Cefuroxime crosses the blood–brain barrier when the meninges are inflamed.

Biotransformation

Cefuroxime is not metabolised.

Elimination

Cefuroxime is excreted by glomerular filtration and renal tubular secretion. The serum half-life after either intramuscular or intravenous injection is approximately 70 minutes. There is almost complete recovery (85 to 90%) of unchanged cefuroxime in urine within 24 hours of administration, with the majority excreted within the first 6 hours. 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 sodium.

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 dose selection, and it may be useful to monitor renal function (see section 4.2).

Paediatrics: The serum half-life of cefuroxime is substantially prolonged in neonates according to gestational age. In older infants (aged > 3 weeks) and 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. In patients with markedly impaired renal function (Clcr < 20 mL/min) the dosage of cefuroxime should be reduced to compensate for its slower excretion (see section 4.2). 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 affect its pharmacokinetics.

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 for interference in clinical laboratory tests in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

The product is a sterile dry powder for injection and does not contain any added excipients.

6.2 Incompatibilities

Cefuroxime should not be mixed in the syringe or giving set with aminoglycosides prior to or during administration.

6.3 Shelf Life

Unopened: 24 months.

Reconstituted solution: The product should be used immediately. If not practicable, the diluted product may be stored for 12 hours if stored at 25°C, or 24 hours if stored at 2–8°C, after which time unused material should be discarded.

6.4 Special Precautions for Storage

Unopened: Do not store above 25°C. Keep the vials in the outer carton.

After reconstitution: Store at 2–8°C.

6.5 Nature and Contents of Container

CEFUROXIME FOR INJECTION USP 750 mg is packed in a 10 mL transparent glass vial, USP Type III, stoppered with a grey bromobutyl rubber stopper and sealed with a red flip-off seal, packed in a printed carton along with the package insert.

6.6 Special Precautions for Disposal

No special requirements.

7. Marketing Authorisation Holder

FINEBIOTICS PHARMA LIMITED

Plot No. 5, Sector-3, SIDCUL,

II-E SIDCUL, Pantnagar, Rudrapur-263153,

Uttarakhand, India.

Manufacturer

FINEBIOTICS PHARMA LIMITED

Plot No. 5, Sector-3, SIDCUL,

II-E SIDCUL, Pantnagar, Rudrapur-263153,

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8. Marketing Authorisation Number

H2022/CTD8290/16077

9. Date of First Authorisation / Renewal of Authorisation

2022 September 21

10. Date of Revision of The Text

2022 September 21