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

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Cefuroxime Injection IP 1.5g/750mg

FERVAY® 1.5g/750mg फ़रवे १.५जि/७५०एमजि

COMPOSITION

FERVAY® 1.5g
Each Vial Contains:
Cefuroxime Sodium IP (Sterile)
Eq. to Cefuroxime 1.5g

FERVAY® 750mg
Each Vial Contains:
Cefuroxime Sodium IP (Sterile)
Eq. to Cefuroxime 750mg

PHARMACEUTICAL FORM
Powder for solution for Injection or Infusion.
Colour of powder varies from white to faintly yellow.
Reconstituted solutions of Fervay range in colour from light yellow to amber colour, depending on the concentration and diluent used.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Pharmacotherapeutic group: second generation cephalosporins
ATC code: J01DC02

Mechanism of Action
Cefuroxime is a bactericidal cephalosporin antibiotic which is resistant to most beta-lactamases and is active against a wide range of Gram-positive and Gram-negative organisms.
Cefuroxime inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs). This in turn inhibits the final trans-peptidation step of peptidoglycan synthesis, essential for bacterial cell wall synthesis. Eventually sensitive bacteria get lysed due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases), while cell wall assembly is arrested.

Pharmacokinetic Properties
Absorption and Distribution
After intramuscular (IM) injection of a 750 mg dose of cefuroxime to normal volunteers, the mean peak serum concentration was 27 mcg/mL and occurred at approximately 45 minutes (range, 15 to 60 minutes). Following intravenous (IV) doses of 750 mg and 1.5 g, serum concentrations were approximately 50 and 100 mcg/mL, respectively, at 15 minutes. Therapeutic serum concentrations of 2 mcg/mL or more were maintained for 5.3 hours and 8 hours or more, respectively. There was no evidence of cefuroxime accumulation in the serum following IV administration of 1.5 g doses every 8 hours to normal volunteers. Cefuroxime is detectable in therapeutic concentrations in pleural fluid, joint fluid, bile, sputum, bone, aqueous humor, and cerebrospinal fluid (CSF) of adults and pediatric patients with meningitis. Cefuroxime is approximately 50% bound to the serum protein.

Metabolism and Excretion
The serum half-life after either IM or IV injections is approximately 80 minutes and is prolonged in neonates and patients with renal impairment. Approximately 89% of a dose of cefuroxime is excreted unchanged by glomerular filtration and renal tubular excretion by the kidneys over an 8-hour period, resulting in high urinary concentrations. A small amount of cefuroxime is excreted in bile.
Following the IM administration of a 750 mg single dose, urinary concentrations averaged 1,300 mcg/mL during the first 8 hours. Intravenous doses of 750 mg and 1.5 g produced urinary levels averaging 1,150 and 2,500 mcg/mL, respectively, during the first 8-hour period.
The concomitant oral administration of probenecid with cefuroxime slows tubular secretion, decreases renal clearance by approximately 40%, increases the peak serum level by approximately 30%, and increases the serum half-life by approximately 30%.

Preclinical Safety Data
No clinically relevant data has been reported. There is no experimental evidence of embryopathic or teratogenic effects attributable to cefuroxime.

CLINICAL PARTICULARS
Therapeutic Indications
Cefuroxime is indicated in the treatment of susceptible infections of lower respiratory tract, urinary tract, skin and soft tissue, bone and joint, septicaemia, meningitis, gonorrhea, caused by staphylococci, group B streptococci, *Haemophilus influenzae* (type A and B), *Escherichia coli, Enterobacter* species, *Salmonella* species, and *Klebsiella* species.
Cefuroxime is an effective prophylactic against post-operative infections. Usually cefuroxime 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 injection. The recommended doses of both antibiotics may be given depending on the severity of the infection and the patient's condition.
Cefuroxime is also available in tablet form as axetil ester for oral administration. This permits the use of sequential therapy with the same antibiotic, when a change from parenteral to oral therapy is clinically indicated. Where appropriate cefuroxime injection is effective when used prior to oral therapy with in the treatment of pneumonia and acute exacerbations of chronic bronchitis.

Posology and Method of Administration
Adults:
The usual recommended dose is 750 mg t.i.d. for IM or IV, for 5 to 10 days. For more severe infections, this dose should be increased to 1.5 g t.i.d. IV. The frequency of administration can be increased to 6-hourly if necessary, giving total daily doses of 3 to 6 g.

Gonorrhoea: 1.5 g should be given as a single dose. This may be given as 2 x 750 mg injections at different sites e.g., each buttock (with oral probenecid 1 g).

Meningitis: Cefuroxime is suitable for sole therapy of bacterial meningitis caused by sensitive strains. Dosage should not exceed 3 g intravenous, every 8 hours.

For preventive use for clean-contaminated or potentially contaminated surgical procedures, a 1.5 g dose is recommended intravenously just before surgery (approximately one-half to 1 hour before the initial incision). Thereafter, a dose of 750 mg IV or IM, every 8 hours when the procedure is prolonged. For preventive use during open-heart surgery, a 1.5 g dose is administered intravenously at the induction of anesthesia and every 12 hours; thereafter for a total of 6 g is recommended.

Infants and Children ≥3 months:
Doses of 30 to 100 mg/kg/day, IM or IV, given as 3 or 4 divided doses. A dose of 60 mg/kg/day will be appropriate for most infections and 100 mg/kg/day for most severe infections. The usual dose for bone and joint infection is 150 mg/kg/day, IM or IV, in divided doses every 8 hours. For treatment of bacterial meningitis, the usual dose is 200 to 240 mg/kg/day IV in 3 or 4 divided doses. This dosage may be reduced to 100 mg/kg/day, IV after 3 days or when clinical improvement occurs.

Elderly: No dosage adjustment recommended.

Sequential therapy:

Pneumonia:
1.5 g b.i.d (IV) for 48 to 72 hours, followed by 500 mg b.i.d., oral therapy for 7 days.

Acute exacerbations of chronic bronchitis:
750 mg b.i.d (IV or IM) for 48 to 72 hours, followed by 500 mg b.i.d., oral therapy for 5 to 7 days.
Duration of both parenteral and oral therapy is determined by the severity of the infection and the clinical status of the patient.

Renal Impairment:
A reduced dosage of cefuroxime must be employed when renal function is impaired. Dosage should be determined by the degree of renal impairment. The recommended dosage regimen of cefuroxime in patients with renal impairment is shown in table 1.

Table 1: Dosage of Cefuroxime in Adults with Renal Impairment

Creatinine Clearance (mL/min)	Dosage
>20	750 mg-1.5 g, every 8 hours
10-20	750 mg, every 12 hours
<10	750 mg, every 24 hours[a]

[a] For patients on haemodialysis, a further 750 mg dose should be given at the end of each dialysis.
When continuous peritoneal dialysis is being used, a suitable dosage is usually 750 mg twice daily.

Contraindications
Cefuroxime is contraindicated in patients with
- Hypersensitivity to cefuroxime or any other component of the formulation; or to the cephalosporin group of antibiotics
- Acute porphyria

Special Warnings and Precautions for Use
Allergic Reactions
Special caution should be taken in patients who have had an experience of allergic reaction to penicillins or beta-lactams. If an allergic reaction to cefuroxime occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

***Clostridium difficile*-Associated Diarrhea**
Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including cefuroxime, and may range in severity from mild diarrhea to fatal colitis. If CDAD is suspected or confirmed, ongoing antibiotic use needs to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *Clostridium difficile*, and surgical evaluation should be instituted as clinically indicated. If antibiotic-associated pseudomembranous colitis produced by *C difficile* is not relieved by drug discontinuation, or when it is severe, oral vancomycin is the treatment of choice.

Diuretics
Although cefuroxime rarely produces alterations in kidney function, evaluation of renal status during therapy is recommended, especially in seriously ill patients receiving the maximum dose. Cephalosporins should be given with caution to patients receiving concurrent treatment with potent diuretics as these regimens are suspected of adversely affecting renal function. The total daily dose of cefuroxime should be reduced in patients with transient or persistent renal insufficiency, because high and prolonged serum antibiotic concentrations can occur in such individuals from usual doses.

Gastrointestinal Disease
Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Nephrotoxicity
Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins.

Hearing Loss
As with other therapeutic regimens used in the treatment of meningitis, mild-to-moderate hearing loss has been reported in a few pediatric patients treated with cefuroxime. Persistence of positive cerebrospinal fluid (CSF) cultures at 18 to 36 hours has also been noted with cefuroxime injection, as well as with other antibiotic therapies; however, the clinical relevance of this is unknown.

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Seizures
Several cephalosporins, including cefuroxime, have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage is not reduced (see **Dosage and Method of Administration** section). If seizures associated with drug therapy should occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Prothrombin Activity
Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, patients with poor nutritional state, patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.

Prophylactic Therapy
Prescribing cefuroxime in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.
As with other antibiotics, prolonged use of cefuroxime may result in the overgrowth of non-susceptible organisms (e.g. *Candida* species, enterococci, *Clostridium difficile*), which may require interruption of treatment.

Drug Interactions
In common with other antibiotics, cefuroxime may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral contraceptives.
As with other cephalosporin antibiotics in combination with potent diuretics such as furosemide or aminoglycosides, cefuroxime may adversely affect renal function (see **Special Warnings and Precautions for Use** section).
Cefuroxime does not interfere in enzyme-based tests for glycosuria. 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. It is recommended that either the glucose oxidase or hexokinase methods are used to determine blood/plasma glucose levels in patients receiving cefuroxime.
Cefuroxime does not interfere in the alkaline picrate assay for creatinine.

Pregnancy and Lactation
Pregnancy category B: Though there are no adequate and well-controlled studies in pregnant women, cefuroxime can be used in pregnant women; but only if clearly needed. Since cefuroxime is excreted in human milk, caution should be exercised when cefuroxime is administered to a nursing woman.

Effects on Ability to Drive and Use Machines
Not applicable

Undesirable Effects
Cefuroxime is generally well tolerated. The most common adverse effects have been local reactions following IV administration. Other adverse reactions have been encountered only rarely. The adverse effects in their frequency of occurrence during clinical trials are as shown in table 2:

Table 2: List of Adverse Effects Reported with their Frequency of Occurrence

Adverse Effect	Greater than or Equal to (≥1)%	Less than (<1)%
Local Reactions	Thrombophlebitis	-
Gastrointestinal	-	Diarrhea, nausea
Hypersensitivity Reactions	-	Rash, pruritus, urticarial, positive Coombs' test, Anaphylaxis, fever, erythema multiforme, interstitial nephritis, toxic epidermal necrolysis, and Stevens Johnsons syndrome
Haematologic	Decreased haemoglobin, haematocrit, transient eosinophilia, transientneutropenia	Leukopenia, thrombocytopenia
Hepatic	Increased SGOT, SGPT, phosphatase, LDH levels.	Increased bilirubin levels

SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; LDH: lactate dehydrogenase.

Post-marketing Experience
The following events have been observed in patients, cutaneous vasculitis, seizure, angioedema, vomiting, abdominal pain, colitis, vaginitis including vaginal candidiasis, toxic nephropathy, cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, prolonged prothrombin time, pancytopenia, agranulocytosis.

Overdose
Overdose of cephalosporins can cause neuromuscular hypersensitivity and convulsions. Elevated serum levels of cefuroxime can be reduced by hemodialysis and peritoneal dialysis. High dose of probenecid decreases the clearance of cefuroxime. Aminoglycosides increase the nephrotoxic potential.

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

Shelf Life: Please refer to carton/label.

Storage and Precautions
Store in a dry place at a temperature not exceeding 25°C, Protect from light.
Keep out of reach of children.

Special Precautions for Disposal and Other Handling
Administer around-the-clock to promote less variation in peak and trough serum levels. Cefuroxime sodium may be administered as direct IV injection, or deep IM injection or IV infusion. The drug should be given IV rather than IM in patients with septicemia or other severe life-threatening infections or in patients with lowered resistance, particularly if shock is present.

Direct intermittent intravenous (IV) injection: Dissolve 750 mg vial content in 6 mL and 1.5 g vial content in 15 mL of sterile water for injections IP to provide solution containing approximately 90 mg/mL of cefuroxime solution. The entire content of the vial should be withdrawn for each dose. The appropriate dose should then be slowly injected directly in to a vein over 3 to 5 minutes or injected directly in to the tubing of a freely flowing compatible IV solution.

Intermittent or continuous intravenous (IV) infusion: For intermittent or continuous IV infusion, the reconstituted solution should be further diluted to 100 mL with 5% dextrose injection or 0.9% sodium chloride injection or other compatible IV solution to get a 7.5 or 15 mg/mL solution of cefuroxime; intermittent IV solutions are generally infused over 15 to 60 minutes.

If aminoglycoside is administered concomitantly with cefuroxime, the drugs should be administered at separate sites. Other IV infusions flowing through a common administration tubing or site should be discontinued while cefuroxime is infused unless the solutions are compatible and the flow rate adequately adjusted. Cefuroxime sodium is incompatible with sodium bicarbonate and should not be diluted with it.

Intramuscular injection: Intramuscular injections are prepared by adding 3 mL of sterile water for injection to the 750 mg of cefuroxime vial so as to provide a suspension containing approximately 220 mg/mL. Shake the suspension gently prior to administration. The entire contents of the vial should be withdrawn for each dose.

Intramuscular injection should be made deeply into a large muscle mass such as the gluteus or lateral aspect of the thigh. The plunger of the syringe should be drawn back before IM injection to ensure that the needle is not in a blood vessel.

Nature and Contents of Container

FERVAY® 1.5 g
Cefuroxime Injection IP 1.5 g supplied as sterile dry powder for injection in 20 mL flint vial in a monocarton, without diluent.

FERVAY® 750 mg
Cefuroxime Injection IP 750 mg supplied as sterile dry powder for injection in 10 mL flint vial in a monocarton, without diluent.

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

BF/LL/3843/01

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Leaflet revised on August 2019

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