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

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Biocon

Cefuroxime Axetil Tablets IP 250 mg
Cefuroxime Axetil Tablets IP 500 mg

FERVAY® 250 / FERVAY® 500 फ़रवे २५० / फ़रवे ५००

COMPOSITION
FERVAY®250
Each film coated tablet contains:
Cefuroxime Axetil IP
Eq. to Cefuroxime 250 mg
Excipients q.s.
Colours: Ferric oxide USP-NF Red, Ferric oxide USP-NF Yellow & Titanium Dioxide IP

FERVAY®500
Each film coated tablet contains:
Cefuroxime Axetil IP
Eq. to Cefuroxime 500 mg
Excipients q.s.
Colours: Ferric oxide USP-NF Red, Ferric oxide USP-NF Yellow & Titanium Dioxide IP

PHARMACEUTICAL FORM
Tablets

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 (PBP's). This in turn inhibits the final trans-peptidation step of peptidoglycan synthesis, essential for bacterial cell wall synthesis. Eventually, the 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

After oral administration, cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolysed in the intestinal mucosa and blood, causing the release of the active compound, cefuroxime, into the circulation.

Effect of food on pharmacokinetics

Absorption of the drug is greater when taken after food (absolute bioavailability of cefuroxime tablets increases from 37% to 52%). The postprandial pharmacokinetics of cefuroxime tablet is given in table 1.

Table 1: Postprandial Pharmacokinetics of Cefuroxime Tablets in Adults[a]

Dose[b] Cefuroxime Equivalent	Peak Plasma Concentration (mcg/mL)	Time of Peak Plasma Concentration (hrs)	AUC (mcg x hr/mL)
250 mg	4.1	2.5	12.9
500 mg	7.0	3.0	27.4

[a] Mean values of 12 healthy volunteers
[b] Drug administered immediately after meal
AUC area under the curve

Distribution
Cefuroxime is widely distributed in the body throughout the extracellular fluids including pleural fluid, sputum, bone, synovial fluid, and aqueous humour, but achieves therapeutic concentrations only in the cerebro spinal fluid (CSF) when the meninges are inflamed. About 50% of cefuroxime in the circulation is bound to plasma proteins. It diffuses across the placenta and has been detected in breast milk.

Metabolism and Elimination
The axetil moiety of cefuroxime axetil is metabolized to acetaldehyde and acetic acid. Cefuroxime is not metabolised and is excreted unchanged. About 50% is excreted by glomerular filtration and about 50% through renal tubular secretion within 24 hours, with the majority being eliminated within 8 hours. Approximately 50% of the administered dose is recovered in the urine within 12 hours. Small amounts of cefuroxime are excreted in bile. The plasma half-life ranges between 60 and 90 minutes and the mean serum half-life in postprandial administration of cefuroxime is about 1.2 hours. As cefuroxime is renally excreted, the serum half-life is prolonged in patients with reduced renal function. Probenecid competes with cefuroxime for renal tubular secretion resulting in higher and more prolonged plasma concentrations of cefuroxime. Dialysis causes the decrease of cefuroxime serum levels.

Preclinical Safety Data
No clinically relevant data has been reported.

CLINICAL PARTICULARS
Therapeutic Indications
Cefuroxime is indicated for the treatment of patients with mild to moderate infections like pharyngitis/tonsillitis, acute bacterial otitis media, acute bacterial maxillary sinusitis, acute bacterial exacerbations of chronic bronchitis and secondary bacterial infections of acute bronchitis, uncomplicated skin and skin-structure infections, uncomplicated urinary tract infections, uncomplicated gonorrhea, early Lyme disease (erythema migrans) caused by streptococci; group B streptococci, *Haemophilus influenzae* (type A and B), *Escherichia coli*, *Enterobacter* species, *Salmonella* species, *Klebsiella* species.

Posology and Method of Administration
The dosage depends on the severity of the infection. For severe infections, parenteral forms of cefuroxime are recommended. Cefuroxime axetil is effective when used following initial parenteral cefuroxime sodium in the treatment of pneumonia and acute exacerbations of chronic bronchitis. In order to achieve optimum absorption, cefuroxime axetil tablets should be taken shortly after meals. The dosage schedule based on the type of infection is given in table 2.

Table 2: Dosage Schedule for Cefuroxime Tablets

Population/Infection	Dose	Duration (days)
Adults and Adolescents(>12 Years)		
Pharyngitis/tonsillitis	250 mg b.i.d	10
Acute bacterial maxillary sinusitis	250 mg b.i.d	10
Acute bacterial exacerbations of chronic bronchitis	250 or 500 mg b.i.d	10[a]
Secondary bacterial infections of acute bronchitis	250 or 500 mg b.i.d	5-10
Uncomplicated skin and skin-structure infections	250 or 500 mg b.i.d	10
Uncomplicated urinary tract infections	250 mg b.i.d	7-10
Uncomplicated gonorrhea	1,000 mg once	single-dose
Early Lyme disease	500 mg b.i.d	20
Paediatric Patients ≥ 3 Months		
Acute otitis media	250 mg b.i.d	10
Acute bacterial maxillary sinusitis	250 mg b.i.d	10

[a] The safety and effectiveness of cefuroxime administered for less than 10 days in patients with acute exacerbations of chronic bronchitis have not been established.

Special Populations
Renal Impairment
The safety and efficacy of cefuroxime in patients with renal failure have not been established. Since cefuroxime is renally eliminated, its half-life will be prolonged in patients with renal failure (see **Pharmacokinetic Properties** section).

Pediatrics
Safety and effectiveness of cefuroxime is not established in infants less than 3 months old.

Geriatrics
Despite the lower elimination of cefuroxime in geriatric patients, dosage adjustment based on age is not necessary (see **Pharmacokinetic Properties** section).

Contraindications
Cefuroxime is contraindicated in patients with:
- Hypersensitivity to cefuroxime, other cephalosporins or to any of the excipients.
- Previous immediate and/or severe hypersensitivity reaction to penicillin or to any other type of beta-lactam medicinal products.

Special Warnings and Precautions for Use
Hypersensitivity reactions
Before therapy with cefuroxime is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefuroxime products, other cephalosporins, penicillins, or other drugs.

If this product is to be given to penicillin-sensitive patients, caution should be exercised because cross-hypersensitivity among betalactam antibiotics has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy.

If a clinically significant allergic reaction to cefuroxime products occurs, discontinue the drug and institute appropriate therapy.

Serious acute hypersensitivity reactions may require treatment with epinephrine and other emergency measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated.

Clostridium difficile associated diarrhea
Clostridium difficile-associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents, including cefuroxime, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *Clostridium difficile.*

Clostridium difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. *Clostridium difficile* associated diarrhea (CDAD) must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over 2 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.

As with other broad-spectrum antibiotics, prolonged administration of cefuroxime may result in the overgrowth of non-susceptible microorganisms. If super-infection occurs during therapy, appropriate measures should be taken.

Diuretics
Cephalosporins, including cefuroxime, should be given with caution to patients

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receiving concurrent treatment with potent diuretics because these diuretics are suspected of adversely affecting renal function.

Gastrointestinal malabsorption
Cefuroxime, as with other broad-spectrum antibiotics, should be prescribed with caution in individuals with a history of colitis. The safety and effectiveness of cefuroxime have not been established in patients with gastrointestinal malabsorption.

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.

Antibiotics
Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as 2 or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Drug Interactions
Concomitant administration of probenecid with cefuroxime tablets increases the serum concentration of cefuroxime by 50%.

Drugs that reduce gastric acidity may result in a lower bioavailability of cefuroxime compared with that of fasting state and tend to cancel the effect of postprandial absorption.

In common with other antibiotics, cefuroxime may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone contraceptives.

Cefuroxime may interfere with the determination of glucose in urine with copper containing reagents (Benedict or Fehling solution, Clinitest). For the determination of blood and plasma sugar levels in patients receiving cefuroxime axetil, the glucose-oxidase or hexokinase method is recommended.

The use of cefuroxime may be accompanied by a false positive Coombs test. This may interfere with the performance of cross matching tests with blood.

Cephalosporin antibiotics at high dosage should be given with caution to patients receiving potent diuretics, aminoglycosides, or amphotericin as these combinations increases the risk of nephrotoxicity.

Since bacteriostatic drugs may interfere with the bactericidal action of cephalosporins, it is advisable to avoid giving tetracyclines, macrolides, or chloramphenicol in conjunction with cefuroxime

Pregnancy and Lactation
Pregnancy category B: There are no adequate and well-controlled studies in pregnant women. Therefore, this drug should be used during pregnancy only if clearly needed. Because, cefuroxime is excreted in human milk, consideration should be given to discontinuing nursing temporarily during treatment with cefuroxime.

Effects on Ability to Drive and Use Machines
There are no studies on the effect of cefuroxime on the ability to drive and to handle machines.

Undesirable Effects
Clinical trials
The adverse effects reported possibly, probably, or almost certainly related to cefuroxime tablets in multiple-dose clinical trials and in 1 g single-dose clinical trials in the treatment of uncomplicated gonorrhea based on their frequency of occurrence are given in table 3 and table 4 respectively.

Table 3: Adverse Effects in Multiple-dose Regimens

Greater than or equal to (≥) 1%	Less than (<) 1% but greater than (>) 0.1%
Diarrhea/loose stools, nausea/vomiting, transient elevation in AST, ALT, LDH, eosinophilia	Abdominal pain, abdominal cramps, flatulence, indigestion, headache, vaginitis, vulvar itch, rash, hives, itch, dysuria, chills, chest pain, shortness of breath, mouth ulcers, swollen tongue, sleepiness, thirst, anorexia, positive coombs test

AST: aspartate transaminase; ALT: alanine transaminase; LDH: lactate dehydrogenase

Table 4: Adverse Effects in 1 g Single-dose Regimen for Uncomplicated Gonorrhea

Greater than or equal to (=) 1%	Less than (<) 1% but greater than (>) 0.1%
Nausea/vomiting, diarrhea	Abdominal pain, dyspepsia, erythema, rash, pruritus, vaginal candidiasis, vaginal itch, vaginal discharge, headache, dizziness, somnolence, muscle cramps, muscle stiffness, muscle spasm of neck, tightness/pain in chest, bleeding/pain in urethra, kidney pain, tachycardia, lockjaw-type reaction

Post-marketing Experience
The adverse effects reported in the post-marketing experience are:
General: anaphylaxis, angioedema, pruritus, rash, serum sickness-like reaction, urticaria
Gastrointestinal: pseudomembranous colitis
Hematologic: hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia, and increased prothrombin time.
Hepatic: hepatic impairment including hepatitis and cholestasis, jaundice
Neurologic: seizure
Skin: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.
Urologic: renal dysfunction.

Cephalosporin-class Adverse Reactions
The following adverse reactions and altered laboratory tests have been reported for antibiotics of the cephalosporin-class: toxic nephropathy, aplastic anemia, hemorrhage, increased blood urea nitrogen (BUN), increased creatinine, false-positive test for urinary glucose, increased alkaline phosphatase, neutropenia, elevated bilirubin, and agranulocytosis.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given, if clinically indicated.

Overdose
Overdosage of cephalosporins can cause cerebral irritation leading to convulsions. Serum levels of cefuroxime can be reduced by hemodialysis and peritoneal dialysis.

PHARMACEUTICAL PARTICULARS
Shelf Life
Please refer to carton/aluminium strip pack

Storage and Precautions
Store below 25° C. Protected from light and moisture.

Keep out of reach of children

Special Precautions for Disposal and Other Handling
No special requirements

Nature and Contents of Container

FERVAY®250: 10 tablets in a Alu-Alu strip packing .10 such strips in a carton, with a package insert.

FERVAY®500: 10 tablets in a Alu-Alu strip packing. 10 such strips in a carton, with a package insert.

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

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BF/LL/3642/01

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To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free number: **1800 102 9465** or e-mail us at **drugsafety@biocon.com.**