Cefuroxime Axetil

Zegen®

250 mg Tablet
500 mg Tablet

ANTIBACTERIAL

FORMULATION
Each tablet contains:
Cefuroxime (as axetil).....250 mg or 500 mg

PRODUCT DESCRIPTION
Cefuroxime (Zegen) 250 mg and 500 mg are white to off-white colored, biconvex, capsule-shaped, film-coated tablets with break line on one side.

CLINICAL PHARMACOLOGY
PHARMACODYNAMICS
Cefuroxime, a semi-synthetic second generation cephalosporin which exerts its bactericidal activity by interfering with the bacterial cell wall synthesis. It binds to specific penicillin-binding proteins responsible for the synthesis of peptidoglycan, a heteropolymeric structure that gives the cell wall its mechanical stability. The final stage of the peptidoglycan synthesis involves the completion of the cross-linking of the terminal glycine residue of the pentaglycine bridge to the fourth residue of the pentapeptide. The transpeptidase that catalyzes this step is inhibited by cephalosporins. As a result, the bacterial cell wall is weakened, the cell swells and then ruptures.

ANTIMICROBIAL SPECTRUM OF ACTIVITY
The *in vivo* bactericidal activity of cefuroxime axetil is due to the parent compound cefuroxime.
Cefuroxime has demonstrated activity against most strains of the following microorganisms both *in vitro* and in clinical infections:

Aerobic Gram-positive	Aerobic Gram-negative	Spirochetes
*Staphylococcus aureus**	*Escherichia coli*	*Borrelia burgdorferi*
Streptococcus pneumoniae	*Haemophilus influenzae**	
Streptococcus pyogenes	*Haemophilus parainfluenzae*	
	Klebsiella pneumoniae	
	*Moraxella catarrhalis**	
	*Neisseria gonorrhoeae**	

**Including beta-lactamase-producing strains*

Cefuroxime has also demonstrated *in vitro* activity against most strains of the following microorganisms; however, clinical significance is unknown:

Aerobic Gram-positive	Aerobic Gram-negative	Anaerobic
Staphylococcus epidermidis	*Morganella morganii*	*Peptococcus niger*
Staphylococcus saprophyticus	*Proteus inconstans*	
Streptococcus agalactiae	*Proteus mirabilis*	
	Providencia rettgeri	

Listeria monocytogenes and certain strains of enterococci, e.g., *Enterococcus faecalis* (formerly *Streptococcus faecalis*), are resistant to cefuroxime. Methicillin-resistant staphylococci are resistant to cefuroxime.

Pseudomonas spp., *Campylobacter* spp., *Acinetobacter calcoaceticus*, *Legionella* spp., and most strains of *Serratia* spp. and *Proteus vulgaris* are resistant to most first- and second-generation cephalosporins. Some strains of *Morganella morganii*, *Enterobacter cloacae*, and *Citrobacter* spp. have been shown by *in vitro* tests to be resistant to cefuroxime and other cephalosporins.

Most strains of *Clostridium difficile* and *Bacteroides fragilis* are resistant to cefuroxime.

PHARMACOKINETICS
The bioavailability of cefuroxime axetil after oral administration is variable and depends on the formulation used. The tablet/capsule formulations should not, therefore, be substituted with powder for oral suspension formulations on a mg/mg basis.

The bioavailability of cefuroxime axetil is significantly increased from 37% to 52% by coadministration with food.

Average peak serum cefuroxime concentrations of 4.1, 7, or 13.6 mcg/mL are attained approximately 2 to 3 hours after oral administration in adults of a single 250 mg, 500 mg or 1 g dose, respectively. Average serum concentrations after 6 hours are 0.7, 2.2, or 3.4 mcg/mL, respectively. The area under the curve (AUC) of the drug averaged 12.9, 27.4, or 50 mcg-hr/mL, respectively.

Cefuroxime's apparent volume of distribution in healthy adults ranges from 9.3 to 15.8 L per 1.73 m^2. Cefuroxime is widely distributed in the body including pleural fluid, sputum, bone, synovial fluid, and aqueous humor, but only achieves therapeutic concentrations in the cerebrospinal fluid when the meninges are inflamed. Cefuroxime is 33-50% protein-bound.

Cefuroxime readily crosses the placenta and can also be detected in human milk.

In adults, the serum or plasma half-life ($t_{\frac{1}{2}}$) after oral administration of cefuroxime axetil ranges from 1.2 to 1.6 hours and about 50% of an administered dose is recovered in the urine within 12 hours.

Following oral administration of cefuroxime axetil, the drug undergoes rapid hydrolysis by nonspecific esterases in the intestinal mucosa and blood to yield the active parent drug cefuroxime, which is released into the systemic circulation.

The axetil moiety of the drug is metabolized to acetaldehyde and acetic acid. Cefuroxime itself is not metabolized and its serum level is much closer to the minimum inhibitory concentration (MIC) of important pathogens than cefuroxime axetil.

Cefuroxime is excreted unchanged primarily in the urine by both glomerular filtration and tubular secretion.

In patients with renal impairment, the serum $t_{\frac{1}{2}}$ of the drug is prolonged and generally ranges from 1.9-16.1 hours depending on the degree of renal impairment.
Cefuroxime is removed by hemodialysis and by peritoneal dialysis.

INDICATIONS
For the treatment of the following infections caused by susceptible microorganisms:
- Upper respiratory tract infections including:
  - Acute sinusitis
  - Acute otitis media
  - Acute tonsillopharyngitis
- Lower respiratory tract infections including:
  - Acute bacterial exacerbations of chronic bronchitis
  - Secondary bacterial infections of acute bronchitis
- Uncomplicated skin and skin structure infections including furunculosis, pyoderma and impetigo
- Uncomplicated urinary tract infections including pyelonephritis
- Uncomplicated gonorrhea
- Early Lyme disease (erythema migrans)
- Step down treatment for infections due to susceptible organisms, initially given antimicrobial therapy, particularly parenteral cefuroxime

DOSAGE AND ADMINISTRATION
In general, most infections in adults and adolescents (13 years and older) will respond to 250 mg every 12 hours. However, for more severe infections, 500 mg every 12 hours may be recommended.

Infections	Recommended Dose (To be taken orally after meals)		Duration of Treatment (days)
	Children 7 to 12 years old (Who can swallow tablet whole)	Adults and Adolescents (13 years and older)	
Acute sinusitis	250 mg every 12 hours	250 mg or 500 mg every 12 hours	10
Acute otitis media	250 mg every 12 hours	500 mg every 12 hours	10
Acute tonsillopharyngitis	250 mg every 12 hours	250 mg or 500 mg every 12 hours	10
Acute bacterial exacerbations of chronic bronchitis	250 mg every 12 hours	250 mg or 500 mg every 12 hours	10*
Secondary bacterial infections of acute bronchitis	250 mg every 12 hours	250 mg or 500 mg every 12 hours	5-10
Uncomplicated skin and skin structure infections	250 mg every 12 hours	250 mg or 500 mg every 12 hours	10
Uncomplicated urinary tract infections	250 mg every 12 hours	250 mg or 500 mg every 12 hours	7-10
Uncomplicated gonorrhea	(-)	1,000 mg once	Single Dose
Early Lyme Disease	250 mg every 12 hours	500 mg every 12 hours	20
	Or, as prescribed by a physician		

*The safety and effectiveness of Cefuroxime axetil administered for less than 10 days in patients with acute exacerbations of chronic bronchitis have not been established.

CONTRAINDICATIONS
Known hypersensitivity to cefuroxime, cephalosphorins, penicillins, or any component of the product.

WARNINGS AND PRECAUTIONS
·**Careful inquiry should be made prior to cefuroxime therapy to determine whether the patient has had previous hypersensitivity reactions to cefuroxime, other cephalosporins, penicillins, or other drugs. Use with caution in penicillin-sensitive patients since cross-sensitivity among beta-lactam antibiotics has been clearly documented and may occur in patients with a history of allergy to penicillin. In case of an allergic reaction to cefuroxime, the drug should be discontinued.**

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

·*Clostridium difficile*-associated diarrhea (CDAD) and colitis have 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 *C. difficile*.

C. 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. 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 two 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.

·**Cefuroxime should not be used in patients with a history of cephalosphorin-associated hemolytic anemia since the recurrence of hemolysis is much more severe.**

If a patient develops anemia anytime during, or within 2 to 3 weeks subsequent to the administration of cefuroxime, the diagnosis of cephalosphorin-associated anemia should be considered and the drug discontinued until the etiology is determined.

Periodic monitoring for signs and symptoms of hemolytic anemia, including measurement of hematological parameters of drug-induced antibody testing is recommended in patients treated with cefuroxime.

·As with other broad-spectrum antibacterial agents, cefuroxime should be used with caution in patients with a history of gastrointestinal disease, particularly colitis.

·Cephalosporins, including cefuroxime, have been associated with the development of seizures, particularly in patients with renal impairment, in whom dosage of the drug was not reduced. If seizures due to cefuroxime develop, the drug should be discontinued and treatment with an anticonvulsant be given as clinically indicated.

·Cephalosporins may be associated with a fall in prothrombin activity. Patients who are at risk are those with renal or hepatic impairment or poor nutritional state, as well as 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.

·The patient's renal function should be carefully monitored when cefuroxime is given concurrently with aminoglycosides and/or diuretics because adverse renal effects may occur [see **Interactions with Other Medicaments].**

·The Jarisch-Herxheimer reaction, a transient immunological reaction lasting 1 to 2 days, has been observed following cefuroxime treatment of Lyme disease. Patients should be reassured that this is a common and usually a self-limiting consequence of antibiotic treatment of Lyme disease.

·Cefuroxime has been used safely in a few patients with porphyria although data are insufficient and experimental evidence of porphyrinogenicity are conflicting.

·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 antibiotic resistance.

·As with other antibacterial agents, long term or repeated use may result in overgrowth of non-susceptible organisms, including fungi.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

The carcinogenic potential of cefuroxime has not been evaluated in long-term animal studies.

No evidence of mutagenicity was observed with cefuroxime in various *in vitro* and *in vivo* test systems, including the mouse lymphoma assay, micronucleus test, and bacterial mutation tests. Cefuroxime produced positive results in the *in vitro* chromosome aberration assay.

There are no adequate and controlled studies using cefuroxime in pregnant women. Cefuroxime axetil has not been studied for use during labor and delivery. Since cefuroxime is distributed into milk, cefuroxime axetil should be used with caution in breastfeeding women.

Effects on Ability to Drive and Use Machines: Since cefuroxime may cause dizziness, patients should be advised to avoid performing tasks which require complete mental alertness such as driving and operating machinery.

INTERACTIONS WITH OTHER MEDICAMENTS
- **Aminoglycosides:** The risk of nephrotoxicity may increase when aminoglycosides and cephalosporins are given concomitantly. This has not been reported with cefuroxime use to date. Monitoring of the patient's renal function is advisable when these drugs are given together.
- **Diuretics:** Studies suggest that the concomitant use of potent diuretics, including furosemide and ethacrynic acid, may increase the risk of renal toxicity with cephalosporins.
- **Oral Antacids:** These drugs may result in lower bioavailability of cefuroxime compared with that of the fasting state and tend to cancel the effect of enhanced postprandial absorption.
- **Oral Contraceptives:** As with other antibacterial agents, cefuroxime may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral contraceptives.
- **Probenecid:** Probenecid, given together with or right before administration of cefuroxime, slows down tubular secretion of cefuroxime and produces higher and more prolonged serum cefuroxime concentrations. This drug interaction is usually used beneficially in treating gonorrhea.

Interference with Laboratory Tests

·A false-positive reaction for glucose in the urine may occur with copper reduction tests (Benedict's or Fehling's solution or with Clinitest® Tablets), but not with enzyme-based tests for glycosuria (e.g., Clinistix®, Tes-Tape®).

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

·The presence of cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

·Positive direct antiglobulin (Coombs') test results have also been reported in a few patients receiving oral cefuroxime; however, it is not clear whether the mechanism of this reaction is immunologic in nature. This phenomenon can interfere with cross matching of blood.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
Pregnancy: (Pregnancy Category B) - Since there are no adequate and well controlled studies to date using cefuroxime in pregnant women, use in pregnancy only if the potential benefit justifies the potential risk to the fetus.
Lactation: Cefuroxime is distributed into human milk and should be used with caution in breastfeeding women.
Children: The safety and efficacy of cefuroxime axetil in children younger than 3 months old have not been established.
Elderly: There are no apparent differences in efficacy and safety of cefuroxime between the elderly and younger adults. However, since elderly patients have increased risk of renal impairment, dose adjustment and renal function monitoring may be necessary.
Renal Impairment: The safety and efficacy of oral cefuroxime axetil in patients with renal impairment have not been established. Since cefuroxime is renally eliminated, its half-life will be prolonged in patients with reduced renal function.

UNDESIRABLE EFFECTS
The following adverse events have been reported with the use of cefuroxime, although in many instances the causal relationship to the drug has not been established:
Dermatologic / Hypersensitivity Reaction: Rash (e.g., morbilliform), hives, erythema, pruritus, urticaria, drug fever, anaphylaxis (very rarely), angioedema, serum sickness-like reaction, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (exanthemic necrolysis), shortness of breath and severe bronchospasm
Gastrointestinal (GI): Diarrhea or loose stools, nausea, vomiting, abdominal pain/cramps, gagging, epigastric burning, epigastric pain/dyspepsia, flatulence, indigestion, GI bleeding, mouth ulcers, swollen tongue, dislike of taste, stomach cramps, anorexia, thirst, GI infection, ptyalism, pseudomembranous colitis
Genitourinary: Urethral pain or bleeding, kidney pain, urinary tract infection, dysuria, acute renal failure/dysfunction, interstitial nephritis, transient increases in blood urea nitrogen (BUN) and serum creatinine concentrations; decreased creatinine clearance; bilateral renal cortical necrosis, vaginitis, vaginal candidiasis, vulvovaginal pruritus, vaginal discharge or irritation, menstrual irregularities
Hematologic: Eosinophilia, neutropenia, hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia, thrombocytosis, lymphocytosis; increased prothrombin time; increased erythrocyte sedimentation rate, decreased hemoglobin and/or hematocrit, positive Coombs' test
Hepatic: Transient elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase, alkaline phosphatase, lactate dehydrogenase (LDH), and bilirubin; jaundice, hepatic impairment including hepatitis and cholestasis, decreased serum albumin and/or total protein
Musculoskeletal: Muscle spasm of the neck, muscle cramps or stiffness, arthralgia/joint pain or swelling
Nervous System: Headache, dizziness, somnolence/ sleepiness, irritable behavior, seizures, myoclonic jerks, generalized hyperexcitability/hyperactivity
Respiratory: Pleural effusion, pulmonary infiltrate, dyspnea or respiratory distress, upper respiratory infection, rhinitis, sinusitis, cough
Cardiovascular: Chest pain or tightness, tachycardia
Other Adverse Effects: Jarisch-Herxheimer reaction in patients treated for Lyme disease, candidiasis/candida overgrowth, mild to severe hearing loss, increased or decreased serum glucose concentration, lockjaw-type reaction, viral illness

OVERDOSE AND TREATMENT
Limited information is available on the acute toxicity of cefuroxime in humans. Overdosage of cephalosporins can cause cerebral irritation leading to convulsions. If acute overdosage occurs, cefuroxime may be removed by hemodialysis or peritoneal dialysis.

STORAGE CONDITIONS
- Store in a cool, dry and dark place at temperatures not exceeding 30°C.
- Keep the product out of sight and reach of children.

CAUTION:
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY
Cefuroxime (Zegen) 250 mg tablet box of 100's (in alu-alu foil blister x 4's): DR-XY38616
Cefuroxime (Zegen) 500 mg tablet box of 60's (in alu-alu foil blister x 4's): DR-XY38617

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

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