UNILAB

Cefuroxime

Zegen®

750 mg Powder for Injection
Intravenous / Intramuscular
Antibacterial (Cephalosporin)

℞

FORMULATION: Each vial contains:
Cefuroxime sodium……..790.73 mg
(Equivalent to 750 mg Cefuroxime)

PRODUCT DESCRIPTION
Cefuroxime is a sterile white or faintly yellow powder contained in a colorless glass vial. When reconstituted for intramuscular use, cefuroxime is an opaque off-white suspension. Cefuroxime solution for intravenous use is clear and yellowish.

PHARMACODYNAMICS
Cefuroxime, a semi-synthetic second generation cephalosporin, has antibacterial activity similar to penicillins, carbacephems and cephamycins. Cefuroxime exerts its bactericidal activity by interfering with the synthesis of the bacterial cell wall. 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. Thus, inhibition of the transpeptidase interrupts peptidoglycan synthesis, causing formation of defective cell walls and osmotically unstable spheroplasts and lysis of the bacteria.

PHARMACOKINETICS
In neonates, a single IM administration of cefuroxime 25 mg/kg resulted in cefuroxime serum concentrations averaging 45 μg/mL, 35 μg/mL and 10.5 μg/mL 30 minutes, 3 hours, and 12 hours after injection, respectively.

Cefuroxime's serum half-life is inversely proportional to age in neonates and children. After IM or IV administration, cefuroxime's serum half-life has been reported to be 5.1 to 5.8 hours in neonates 3 days or younger, 2 to 4.2 hours in neonates 6 to 14 days, and 1 to 1.5 hours in neonates 3 to 4 weeks old.

In healthy adults with normal renal function, a single intramuscular (IM) injection of cefuroxime sodium 500-mg, 750-mg, or 1-g dose results in peak serum concentrations of 20.8 to 25.7, 26 to 34.9, and 32 to 40 μg/mL, respectively, attained within 15 to 60 minutes. A single 500- or 750-mg dose given as intravenous (IV) infusion for 30 minutes results in peak serum cefuroxime concentrations averaging 37.8 and 51.1 μg/mL, respectively.

Mean peak serum cefuroxime concentrations and areas under the concentration-time curve (AUC) attained after IM injection is almost similar to those attained after oral administration. Cefuroxime's AUC is proportional to the administered dose and is also similar after IM or IV administration.

Cefuroxime is widely distributed into body tissues and fluids including the kidneys, heart, gallbladder, liver, prostatic adenoma tissue, uterine and ovarian tissue, aqueous humor, saliva, sputum, bronchial secretions, bone, bile, adipose tissue, wound exudates, peritoneal fluid, ascitic fluid, synovial fluid, pericardial fluid, and pleural fluid after IM or IV administration. Therapeutic concentrations of cefuroxime may be attained in cerebrospinal fluid after IV administration in patients with inflamed meninges; however, only low concentrations are attained if the meninges are uninflamed.

Cefuroxime has a protein binding of 33% to 50%.

Cefuroxime readily crosses the placenta. It is also found in amniotic fluid at concentrations averaging 17 to 18.6 μg/mL after a single 750-mg IM dose. Cefuroxime is distributed in breast milk.

ANTIMICROBIAL SPECTRUM OF ACTIVITY
Cefuroxime has demonstrated activity against most strains of the following microorganisms both *in vitro* and in clinical infections:

Aerobic Gram-Positive Microorganisms	*Staphylococcus aureus* (including beta-lactamase producing strains) *Streptococcus pneumoniae* *Streptococcus pyogenes*
Aerobic Gram-Negative Microorganisms	*Escherichia coli* *Haemophilus influenzae* (including beta-lactamase – producing strains) *Haemophilus parainfluenzae* *Klebsiella pneumoniae* *Moraxella catarrhalis* (including beta-lactamase – producing strains) *Neisseria gonorrhoeae* (including beta-lactamase – producing strains)
Spirochetes	*Borrelia burgdorferi*

Cefuroxime has shown activity *in vitro* against most strains of the following microorganisms; however, the safety and effectiveness of cefuroxime in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic Gram-Positive Microorganisms	*Staphylococcus epidermidis* *Staphylococcus saprophyticus* *Streptococcus agalactiae*
Aerobic Gram-Negative Microorganisms	*Morganella morganii* *Proteus inconstans* *Proteus mirabilis* *Providencia rettgeri*
Anaerobic Microorganisms	*Peptococcus niger*

Methicillin-resistant *Staphylococcus aureus* (MRSA) and Enterococci, e.g., *Enterococcus faecalis* (formerly Streptococcus faecalis), are resistant to cefuroxime.

Pseudomonas spp., *Campylobacter* spp., *Acinetobacter calcoaceticus*, 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.

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

INDICATIONS
For the treatment of the following infections caused by susceptible microorganisms:

- Upper respiratory tract infections including ear, nose and throat infections, such as otitis media, sinusitis, tonsillitis, and pharyngitis
- Lower respiratory tract infections including pneumonia, acute bronchitis and acute exacerbations of chronic bronchitis
- Genitourinary tract infections including pyelonephritis and gonorrhea
- Skin and soft tissue infections including furunculosis, pyoderma and impetigo
- Septicemia
- Meningitis
- Bone and joint infections

For surgical prophylaxis (e.g., biliary, gastroduodenal, cardiovascular or orthopedic surgery)

DOSAGE AND ADMINISTRATION
Cefuroxime sodium may be given intravenously (IV) or by deep intramuscular (IM) injection into a large muscle mass (such as the gluteus or lateral part of the thigh). Before IM injection, aspiration is necessary to avoid inadvertent injection into a blood vessel.

For the treatment of septicemia and other severe, life-threatening infections or in immunocompromised patients, especially when shock is present, IV administration is recommended rather than IM.

Treatment of chronic urinary tract infection requires monitoring of bacteriological and clinical response even after therapy has been completed. Persistent infections may require several weeks of treatment. Doses smaller than recommended should not be used to prevent development of antimicrobial resistance.

In staphylococcal and other infections, surgical drainage should be carried out when indicated.

• **Usual Adult Dose**: 750 mg to 1.5 g every 6 to 8 hours for 2 to 10 days depending on the type and severity of infection.

Indications	Dose
• Uncomplicated urinary tract infections* • Skin and skin structure infections* • Disseminated gonococcal infections* • Uncomplicated pneumonia*	750 mg IV every 8 hours In severe infections, 1.5 g IV every 8 hours
• Bone and joint infections*	1.5 g IV every 8 hours
• Bacterial meningitis*	3 g IV every 8 hours
• Life-threatening infections or infections due to less susceptible organisms*	1.5 g IV every 6 hours
* When clinically appropriate, patients may shift to oral antibiotic therapy after IV dose as recommended by a physician.	
• Uncomplicated gonococcal infections	1.5 g IM as a single dose which may be given at two different sites + 1 g oral probenecid
• Surgical prophylaxis**: - Biliary surgery - Cardiac surgery - Vascular surgery - Orthopedic surgery	 1.5 g IV single dose 1.5 g pre-operatively then 1.5 g IV every 12 hours for 48 hours 1.5 g pre-operatively then 1.5 g IV every 8 hours for 24 hours 1.5 g pre-operatively then 750 mg IV every 8 hours for 24 hours
**Cefuroxime should be given within 2 hours before initial incision to ensure adequate tissue cefuroxime concentrations. If the procedure extends to more than 4 hours or major blood loss occurs, it is advisable to administer one or more additional doses during the procedure. It is usually advised that intraoperative doses be administered every 4 to 8 hours for the duration of the procedure.	

• **Usual Pediatric Dose:** 50 to 150 mg/kg body weight per day given IV in 3 to 4 divided doses 2 to 10 days depending on the type and severity of infection.

When clinically appropriate, patients may shift to oral antibiotic therapy as recommended by a physician.

Age Group	Mild to Moderate Infections (50 mg/kg/day)		Severe Infections (100 mg/kg/day)	
	Total Daily Dose (mg)	Dose every 6 to 8 hours	Total Daily Dose (mg)	Dose every 6 to 8 hours
3 to 6 mos	375	125 mg	750	250 mg
6 to 9 mos	500	125 mg	1125	375 mg
10 to 24 mos	750	250 mg	1500	500 mg
2 to 8 yrs	1000	250 mg	2250	500 mg
6 to 10 yrs	1500	500 mg	3000	750 mg
10 to 12 yrs	2250	750 mg	4500	1500 mg

• **For patients with impaired renal function**
Dosage should be determined based on the degree of renal impairment and the susceptibility of the causative organism.

For patients with creatinine clearances greater than 20 mL/minute, dose modification may not be necessary. However, in patients with creatinine clearance of 20 mL/minute or less, doses and/or frequency of administration of cefuroxime must be adjusted based on the degree of renal impairment, severity of infection, and susceptibility of the causative organism as deemed necessary by the doctor.

The frequency of administration of parenteral cefuroxime should be modified as shown below:

Creatinine Clearance (mL/min)	Dose (IV)	Frequency
>20	750 mg to 1.5 g	Every 8 hours
10 to 20	750 mg	Every 12 hours
<10	750 mg	Every 24 hours*

* Patients undergoing hemodialysis should be given another dose of cefuroxime at the end of the dialysis.

Continue treatment for a minimum of 48 to 72 hours after the patient becomes asymptomatic or after evidence of bacterial eradication has been obtained.

DIRECTIONS FOR RECONSTITUTION AND PARENTERAL ADMINISTRATION

Route of Administration	Volume of Sterile Water for Injection	Directions
IM	3 mL	Shake the suspension gently until an opaque suspension is formed before administration and withdraw all the contents of the vial for each IM dose.
Direct IV	8 mL	Slowly inject the solution into a vein or slowly inject into the tubing of a freely flowing compatible IV solution over a 3-5 minute period.
IV Infusion	50 – 100 mL	For short IV infusion (e.g., up to 30 minutes), 750 mg – 1.5 g may be dissolved in 50 to 100 mL Sterile water for injection. This solution may be given directly into the vein or introduced into the tubing of the IV set if the patient is receiving parenteral fluids.

COMPATIBILITY, STORAGE AND STABILITY
When reconstituted as directed with Sterile Water for Injection, cefuroxime suspension for IM injection maintains satisfactory potency for 24 hours at room temperature and for 48 hours under refrigeration (5°C). Discard any unused suspension after the above-mentioned storage periods.

After reconstitution with Sterile Water for Injection, cefuroxime sodium solutions containing 90 to 100 mg cefuroxime per mL or suspensions containing 200 to 220 mg cefuroxime per mL are stable for 24 hours at room temperature and for 48 hours under refrigeration (5°C). More dilute solutions such as 750 mg or 1.5 g dissolved in 100 mL of Sterile Water for Injection, 5% Dextrose Injection, or 0.9% Sodium Chloride Injection, also maintain satisfactory potency for 24 hours at room temperature or for 7 days under refrigeration (5°C).

These solutions may be further diluted to 1-30 mg cefuroxime per mL in the following intravenous solutions and will be stable for 24 hours at room temperature or for 7 days under refrigeration:

- 0.9% Sodium Chloride Injection
- 1/6 M Sodium Lactate Injection
- Ringer's Solution, USP
- Lactated Ringer's Solution, USP
- 5% Dextrose and 0.2% Sodium Chloride Injection
- 5% Dextrose and 0.9% Sodium Chloride Injection
- 5% Dextrose and 0.45% Sodium Chloride Injection
- 5% Dextrose Injection
- 10% Dextrose Injection
- 10% Invert Sugar in Water for Injection

The compatibility of aminoglycosides and cefuroxime sodium depends on several factors such as concentrations of the drugs, specific diluents used, resulting pH, and temperature. If these drugs are to be given concomitantly, it is advised that the drugs be administered at separate infusion sites.

Inspect parenteral drug products visually for particulate matter and discoloration before administration whenever solution and container permit. Like other cephalosporins, cefuroxime powder as well as solutions and suspensions tend to darken, depending on storage conditions, without adversely affecting product potency.

CONTRAINDICATIONS
Known hypersensitivity to cephalosporins, penicillins and other components of the product.

WARNINGS AND PRECAUTIONS
A thorough inquiry about the patient's previous hypersensitivity history should be made. Cefuroxime, like other cephalosporins, penicillins and other drugs, may cause serious hypersensitivity reactions and should be used with caution in any patient who has demonstrated some allergy to any drug. Although it has not been established, allergic reactions to antibiotics may occur more frequently in atopic individuals.

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

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. *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. Careful medical history is necessary because CDAD can occur over two months after administration of antibacterial agents. If CDAD is suspected or confirmed, discontinue ongoing antibiotic use not directed against *C. difficile*. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

GENERAL
As with other broad-spectrum antibiotics, cefuroxime should be given with caution in individuals with a history of colitis. The safety and efficacy of cefuroxime have not been established in patients with gastrointestinal malabsorption.

Cephalosporins may be associated with a fall in prothrombin activity. Patients who are at risk are those with kidney or liver 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.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies have not been performed to date to evaluate the carcinogenic potential of cefuroxime.

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

Reproduction studies in mice and rabbits using cefuroxime sodium in dosages up to 14 and 9 times the usual human dosage, respectively, based on mg/m^2 have not revealed evidence of impaired fertility.

DRUG INTERACTIONS
• 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.

• 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.

• Other Drugs
The patient's renal function should be carefully monitored when cefuroxime is given concurrently with diuretics because adverse renal effects may occur.

Drug/Laboratory Interactions
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™). 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; it is not clear whether the mechanism of this reaction is immunologic in nature.

Transient increases in blood urea nitrogen (BUN) and/or serum creatinine concentrations and decreased creatinine clearance have been reported with cefuroxime use, although causal relationship has not been established.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

PREGNANCY AND LACTATION

Pregnancy: (Pregnancy Category B) Since there are no adequate and well controlled studies to date using cefuroxime in pregnant women, cefuroxime sodium should only be used during pregnancy when clearly needed and when the benefits justify the potential risks.

Lactation: Cefuroxime is distributed into human milk and should be used with caution in breastfeeding women.

Use in children: Cefuroxime's serum half-life is inversely proportional to age when given in children and neonates.

UNDESIRABLE EFFECTS
Dermatologic and Hypersensitivity Reactions: Rash (e.g., morbilliform), fever, pruritus, erythema, urticaria, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, serum sickness-like reactions, angioedema, and anaphylaxis

Gastrointestinal Effects Nausea, vomiting, diarrhea or loose stools, strong, persistent, bitter taste; gagging, burning epigastric pain, gastrointestinal bleeding; flatulence; gastrointestinal infection; ptyalism; indigestion; mouth ulcers; swollen tongue; anorexia; thirst; dyspepsia, and stomach cramps

Hematologic Effects Decreased hematocrit and hemoglobin concentration; transient eosinophilia and neutropenia; pancytopenia; thrombocytopenia; leucopenia; thrombocytosis; lymphocytosis; hemolytic anemia, and increased prothrombin time

Central Nervous System Effects: Headache, dizziness, somnolence or sleepiness; hyperactivity, irritable behavior; seizures, myoclonic jerks, and generalized hyperexcitability

Hepatic Effects: Jaundice; transient increases in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, lactate dehydrogenase (LDH), and bilirubin concentrations

Renal and Genitourinary Effects: Acute renal failure and interstitial nephritis have been reported rarely in patients receiving cefuroxime.

Bilateral renal cortical necrosis that appeared to be a hypersensitivity reaction has occurred in one patient receiving oral cefuroxime. Urinary tract infection, kidney pain, urethral pain or bleeding, dysuria; vaginitis, vaginal candidiasis; vulvovaginal pruritus, and vaginal discharge or irritation have also been reported with oral cefuroxime.

Other Effects: Jarisch-Herxheimer reaction has occurred in patients receiving oral cefuroxime for the treatment of Lyme disease. Mild to severe hearing loss has been reported in a few pediatric patients receiving cefuroxime. Muscle spasm of the neck, muscle cramps or stiffness, chest pain or tightness, shortness of breath, upper respiratory infection, sinusitis, fever, cough, lockjaw-type reaction, viral illness, tachycardia, chills, sinusitis, fever, cough, joint swelling, and arthralgia have been reported in less than 1% of patients receiving oral cefuroxime. Diaper rash has been reported in 3.4% of pediatric patients receiving oral cefuroxime.

OVERDOSAGE & MANAGEMENT
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.

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at +632-**8-UNILAB-1** (+632-**8-864522-1**) for Metro Manila or toll-free +1-800-10-UNILAB-1 for provinces, or e-mail productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

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

AVAILABILITY: Type I clear glass vial (box of 1's)

STORE AT TEMPERATURES NOT EXCEEDING 30° C.

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No. 66 United Street, Mandaluyong City, Metro Manila, Philippines

DR-XY27790
Reg. IPOPHIL
Date of Revision: 10/2021
Date of First Authorization: 08/2002
UA141631IN03

251502673

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