

## ZILISTEN

### Cefuroxime sodium

**COMPOSITION:** Vials containing Cefuroxime Sodium equivalent to Cefuroxime 750mg or 1.5g. Zilisten contains approximately 54.2mg (2.4mEq) of sodium per gram of cefuroxime activity.

**DESCRIPTION:** White to faintly yellow powder which forms a light yellow to amber solution on reconstitution. The reconstituted solution is unstable to light and oxygen.

**ACTIONS AND PHARMACOLOGY:** Cefuroxime is a broad-spectrum cephalosporin which is bactericidal against a wide range of gram-positive and gram-negative organisms. Its bactericidal activity is due to inhibition of cell wall synthesis. It is very stable against beta-lactamases of certain gram-negative organisms.

Peak serum concentrations of cefuroxime are achieved at about 45 min after intramuscular injection. Administration of 750mg and 1.5g intravenously produces serum concentrations of 50mcg/ml and 100mcg/ml respectively at 15 minutes. Therapeutic concentrations of approximately 2mcg/ml or more were maintained for 5 and 8 hours or more respectively. Serum half-life after intramuscular or intravenous administration is approximately 80 minutes.

Cefuroxime is mainly excreted by the kidneys and high urinary concentrations are achieved after both intramuscular and intravenous injections. Concurrent administration of oral probenecid slows excretion rate increases serum half-life and increases peak serum level. Therapeutic concentrations of cefuroxime are achievable in pleural fluid, joint fluid, bile, sputum, bone, cerebrospinal fluid (in patients with meningitis), and aqueous humor. Cefuroxime is approximately 50% bound to plasma protein.

Cefuroxime is effective either alone or in combination with an aminoglycoside, or metronidazole, especially for prophylaxis in colonic surgery. In severe infections, the recommended doses of both antibiotics may be used. Cefuroxime may also be administered pre-operatively as prophylaxis against post-operative infections in patients undergoing surgical procedures which are considered clean-contaminated or potentially contaminated procedures.

**MICROBIOLOGY:** Cefuroxime is usually active against the following organisms in vitro:

Gram-negative: Haemophilus influenzae (including ampicillin-resistant strains), Haemophilus parainfluenzae, Neisseria gonorrhoeae (including penicillinase and non-penicillinase producing strains), Neisseria meningitidis, Escherichia coli, Klebsiella sp. (including K.pneumoniae), Enterobacter sp., Citrobacter sp., Salmonella sp., Shigella sp., Proteus mirabilis, Proteus inconstans, Providencia rettgeri, Morganella morganii.

Some strains of M.morganii, Enterobacter cloacae and Citrobacter sp.have been shown to be resistant to cephalosporins including cefuroxime. Gram-positive - Staphylococcus aureus (including penicillinase- and non-penicillinase-producing strains, Staphylococcus epidermidis and certain strains of Streptococci (eg Strep.pyogenes, Strep.pneumoniae). Certain strains of enterococci are resistant. Anaerobic organisms - Gram-positive and gram-negative cocci (including Peptococcus and Peptostreptococcus sp.), gram-positive bacilli (including Clostridium sp.), gram-negative bacilli (including Bacteroides and Fusobacterium sp.). Most strains of Bacteroides fragilis are resistant. Other bacterial strains resistant to cephalosporins include: Pseudomonas and Campylobacter sp., Acinetobacter cacoaceticus, most strains of Serratia and Proteus vulgaris, methicillin-resistant staphylococci, Clostridium difficile and Listeria monocytogenes.

**INDICATIONS:** Zilisten is indicated for the treatment of infections caused by susceptible organisms in:

Lower respiratory tract infections - Urinary tract infections - Skin and skin structure infections - Septicemia - Meningitis - Gonorrhoea - Bone and joint infections.

Appropriate cultures and susceptibility studies should be performed to determine the susceptibility of the causative organisms to Zilisten. Zilisten may be used together with an aminoglycoside. If so indicated by the severity of the infection and the patient's condition, the recommended dosage of both antibiotics may be given.

Prophylaxis - Zilisten may be given pre-operatively to reduce the incidence of postoperative infections in patients undergoing certain surgical procedures. Zilisten should usually be administered 1/2 to 1 hour before the operation.

**CONTRAINDICATIONS:** Cefuroxime is contraindicated in patients with known allergy to cephalosporins.

**WARNINGS:** Zilisten should be given with caution to patients who have had previous hypersensitivity reactions to penicillin or other drugs.

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with Zilisten, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, Zilisten must be discontinued immediately and appropriate alternative therapy instituted. Serious acute hypersensitivity reactions may require treatment with adrenaline and other emergency measures.

Treatment with broad spectrum antibiotics may alter normal flora of colon and encourages overgrowth of clostridia. Pseudomembranous colitis has been reported. Mild cases of colitis may respond to discontinuation of drug alone. In moderate to severe cases, other measures including fluid and electrolyte replacement and oral vancomycin may be necessary.

**PRECAUTIONS:** Cephalosporins at high dosage should be given with caution to patients receiving concurrent treatment with aminoglycosides and potent diuretics such as frusemide, as these combinations are suspected of adversely affecting renal function. Clinical experience with cefuroxime indicated that this is unlikely at the recommended dosage. Nevertheless, assessment of renal function should be performed during therapy especially in seriously-ill patients who are receiving high doses of the drug.

Dosage of Zilisten should be adjusted in patients with impaired renal function.

Prolonged therapy with Zilisten may result in superinfection with nonsusceptible organisms. It should be used with caution in patients with a history of gastrointestinal disease, especially colitis.

Use in pregnant and lactation mothers - As with all drugs, Zilisten should be used during pregnancy only if clearly indicated. The drug is excreted in breast milk, and should be administered with caution to nursing mothers.

Use in children - Safety and efficacy in children below the age of 3 months have not been established. Accumulation and prolongation of drug half-life in newborn infants have been reported with other cephalosporins.

Interference with laboratory tests - A false-positive reaction for glucose may occur with copper reduction tests eg Benedict's or Fehling's solution or with Clinitest tablets. However, enzyme-based tests for glycosuria are not affected.

**DRUG INTERACTIONS:** See Precautions.

**ADVERSE REACTIONS:** Cefuroxime is generally well-tolerated, the most common adverse effect being thrombophlebitis after intravenous administration. Other adverse effects reported rarely include gastrointestinal symptoms (diarrhea, nausea, pseudomembranous colitis), hypersensitivity reactions (skin rashes, pruritus, urticaria, erythema multiforme, Stevens-Johnson syndrome, anaphylaxis), transient eosinophilia, blood dyscrasias, prolonged prothrombin time, transient rise in liver enzymes, increase in serum creatinine and blood urea nitrogen. Positive Coomb's test with cephalosporin therapy has been reported.

**DOSAGE AND ADMINISTRATION:** Usual adult dose: 750mg to 1.5g every 8 hours for 5 to 10 days. The higher dose range is recommended for severe or complicated infections.

In bone and joint infections, the recommended dose is 1.5g every 8 hours. Surgical intervention should be performed when indicated. Oral antibiotic therapy should be administered when appropriate after completion of a course of parenteral cefuroxime.

In bacterial meningitis, the dose should not exceed 3.0g every 8 hours. For uncomplicated gonococcal infection, the recommended dose is 1.5g intramuscularly as a single dose at two different sites together with oral probenecid 1.0g.

For prophylaxis of postoperative infections, 1.5g is administered intravenously approximately 1/2 to 1 hour prior to the operation, followed by 750mg intravenously or intramuscularly every 8 hours if the procedure is prolonged. For preventive use during open heart surgery, a 1.5g dose given intravenously at the induction of anaesthesia and every 12 hours thereafter for a total of 6.0g is recommended.

Impaired renal function.

Dosage should be adjusted according to the following table:

Creatinine Clearance (ml/min)	Dose	Frequency
> 20	750mg – 1.5g	Every 8 hours
10-20	750mg	Every 12 hours
< 10	750mg	Every 24 hours

Cefuroxime is removed by dialysis and patients on haemodialysis should be given a further dose at the end of the dialysis.

The following should be observed with cefuroxime therapy:

(a) Cefuroxime therapy should be continued for at least 48 hours to 72 hours after the patient becomes asymptomatic or after evidence of bacterial eradication is obtained.

(b) Infections caused by S.pyogenes should be treated for a minimum of 10 days to prevent risk of rheumatic fever or glomerulonephritis.

(c) Treatment of chronic urinary infection should be accompanied by frequent bacteriologic and clinical evaluation and may be required for several months after completion of therapy. For persistent infections, treatment for several weeks may be necessary and doses below the recommended level should not be used.

(d) In infections where there is pus collection, surgical drainage should be performed when indicated.

Infants and children above 3 months of age.

Recommended dose is 50 to 100mg/kg/day in equally divided doses every 6 to 8 hours which is effective for most infections. For more severe infections, the higher dose of 100mg/kg/day should be used but must not exceed the maximum adult dose.

In bacterial meningitis, Zilisten may be given in higher doses, starting with 200 to 240mg/kg/day intravenously in divided doses every 6 to 8 hours.

In children with renal insufficiency, the frequency of dosage should be adjusted as recommended for adults.

#### **Preparation of solution and suspension**

**Zilisten 750mg:** *For intramuscular use:* Add 3.0ml of Sterile Water for Injection. Shake gently to disperse and withdraw 3.6ml of the resulting suspension for injection. *For intravenous use:* Add 8.0ml of Sterile Water for Injection. Shake gently to disperse and withdraw 8.0ml of the resulting solution for injection.

**Zilisten 1.5g:** *For intravenous use:* Add 15.0ml of Sterile Water for Injection. Shake gently and use the resulting solution for injection.

**Administration:** Intramuscular route: Should be administered by deep intramuscular injection into a large muscle mass eg the gluteus or lateral part of the thigh. Care must be taken to avoid inadvertent injection into a blood vessel.

Intravenous route: Preferred route in patients with severe or life-threatening infections, or in poor-risk patients. May be given by: *Direct intermittent intravenous administration* - Inject slowly into a vein over 3 to 5 minutes or injected through a tubing system by which the patient is also receiving other intravenous solutions.

*Intermittent intravenous infusion with a Y-Type administration set* - Solution should be administered through a tubing system by which the patient is also receiving other intravenous solutions. It is recommended to stop administration of other solutions at the same site when infusing solution containing Zilisten.

*Continuous intravenous infusion* - Reconstituted solutions of Zilisten may be added to the following intravenous infusion fluids: 0.9% Sodium Chloride, 5% Dextrose, 10% Dextrose, 5% Dextrose and 0.9% Sodium Chloride, 5% Dextrose and 0.45% Sodium Chloride and M/6 Sodium Lactate.

Solutions of Zilisten should not be added to solutions of aminoglycoside antibiotics because of potential interaction. However, concurrent therapy with Zilisten and an aminoglycoside may be administered separately to the same patient.

**Compatibility and Stability:** Suspensions of Zilisten for intramuscular injection is stable for 5 hours at 25°C and for 48 hours under refrigeration at 4°C. Any unused suspensions must be discarded after the recommended period.

Solutions of Zilisten for intravenous injection are stable for 5 hours at 25°C and for 48 hours under refrigeration at 4°C. More dilute solutions such as 750mg or 1.5g reconstituted with 50 to 100ml of a compatible intravenous infusion fluid maintain satisfactory potency for 24 hours at 25°C and for 72 hours under refrigeration at 4°C. Further dilutions of these solutions to concentrations of between 1mg/ml and 30mg/ml in the following solutions will not lose more than 10% activity for 24 hours at room temperature and for at least 7 days under refrigeration: 0.9% Sodium Chloride, 5% Dextrose, 10% Dextrose, 5% Dextrose and 0.9% Sodium Chloride, 5% Dextrose and 0.45% Sodium Chloride, 5% Dextrose and 0.225% Sodium Chloride, 10% Invert Sugar in Water for injection, M/6 Sodium Lactate, Ringer's Injection USP, Lactated Ringer's Injection USP.

**Unused solutions should be discarded after the recommended stability period.**

Zilisten is also compatible for 24 hours at room temperature when admixed in intravenous infusion with Heparin (10 and 50 units/ml) in 0.9% Sodium Chloride or Potassium Chloride (10 and 40mEq/L) in 0.9% Sodium Chloride Injection.

Note: Prior to administration, parenteral solutions should be inspected visually for particulate matter and discoloration. As with other cephalosporins, cefuroxime powder, suspensions and solutions may darken on storage but this does not affect product potency.

**OVERDOSAGE & TREATMENT:** Overdosage of cephalosporins can cause cerebral irritation leading to convulsions. Symptomatic management should be instituted: protect the patient's airways and support ventilation and perfusion, monitor the vital signs, blood gases, serum electrolytes etc.

Anticonvulsant therapy may be administered if clinically indicated. Serum levels of cefuroxime can be reduced by haemodialysis or peritoneal dialysis.

**STORAGE:** Store dry powder at room temperature at 30°C. Protect from light. Shelf-life: 2.5 years.

**NATURE AND COMPONENTS OF THE CONTAINER:** The products Zilisten 750mg and Zilisten 1.5g are packed in glass vials and in carton boxes of 10 and 50 vials. An instruction leaflet is also included within the box.

**DATE OF LAST REVISION OF THE TEXT:** 2th December 2024.

**PRESENTATION:** Zilisten is supplied in colorless glass vials of:

- 750mg Reg. No.: MAL19961891AZ

- 1.5 g Reg. No.: MAL19961890AZ

