

Zepilen

Cefazolin sodium Ph Eur equivalent to Cefazolin 500mg and 1g

Presentation

ZEPILEN 500mg and 1g vials contain a white to off-white powder which reconstitutes with Sterile Water for Injection to give a colourless solution.

ZEPILEN 500mg vial contains cefazolin sodium equivalent to 500mg of cefazolin.

ZEPILEN 1g vial contains cefazolin sodium equivalent to 1g of cefazolin.

Uses

Actions

ZEPILEN is a semisynthetic cephalosporin for intramuscular or intravenous administration. *In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell-wall synthesis.

ZEPILEN is active against the following organisms *in vitro* and in clinical infections:

Staphylococcus aureus (including penicillinase-producing strains)

Staphylococcus epidermidis. (Methicillin-resistant staphylococci are uniformly resistant to ZEPILEN).

Group A β -haemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant).

Streptococcus pneumoniae

Escherichia coli

Klebsiella sp.

Proteus mirabilis

Haemophilus influenzae

Enterobacter aerogenes

Most strains of indole-positive *Proteus* (*Proteus vulgaris*), *Enterobacter cloacae*, *Morganella morganii*, and *Providencia rettgeri* are resistant.

Serratia, *Pseudomonas* and *Acinetobacter calcoaceticus* (formerly *Mima* and *Herellea* sp.) are almost uniformly resistant to cefazolin.

Disc Susceptibility Tests:

Quantitative methods that require measurements of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure has been recommended for use with discs for testing susceptibility to cefazolin. With this procedure, a report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "moderately susceptible" suggests that the organism would be susceptible if high dosage is used or if the infection were confined to tissues and fluids (e.g. urine) in which high antibiotic levels are attained.

For gram-positive isolates, a zone of 18mm is indicative of a cefazolin-susceptible organism when tested with either the cephalosporin-class disc (30 micron cephalothin) or the cefazolin disc (30 micron cefazolin).

Gram-negative organisms should be tested with the cefazolin disc (using the above criteria) because cefazolin has been shown by *in vitro* tests to have activity against certain strains of *Enterobacteriaceae* found to be resistant when tested with the cephalothin disc. When using the cephalothin disc, Gram-negative organisms with zone diameters ≥ 18 mm may be considered susceptible to cefazolin.

The cefazolin disc should not be used for testing susceptibility to other cephalosporins.

Dilution Techniques:

A bacterial isolate should be considered susceptible if the minimal inhibitory concentration (MIC) for cefazolin is ≤ 16 mcg/mL. Organisms are considered resistant if the MIC is ≥ 64 mcg/mL.

Resistance

Methicillin-resistant staphylococci are uniformly resistant to cefazolin. Most strains of indole-positive *Proteus* (*Proteus vulgaris*), *Enterobacter cloacae*, *Morganella morganii*, and *Providencia rettgeri* are resistant. *Serratia*, *Pseudomonas* and *Acinetobacter calcoaceticus* (formerly *Mima* and *Herellea* sp.) are almost uniformly resistant to cefazolin.

Pharmacokinetics

Table 1 demonstrates the blood levels and duration of cefazolin following intramuscular administration.

Table 1 – Serum concentrations after intramuscular administration.

Dose	Serum Concentrations (mcg/mL)					
	½ Hr	1 Hr	2 Hr	4 Hr	6 Hr	8 Hr
250mg	15.5	17	13	5.1	2.5	
500mg	36.2	36.8	37.9	15.5	6.3	3
1g*	60.1	63.8	54.3	29.3	13.2	7.1

* Average of 2 studies

Clinical pharmacology studies in patients hospitalised with infections indicate that cefazolin produces mean peak serum levels approximately equivalent to those seen in normal volunteers.

In a study (using normal volunteers) of constant intravenous infusion with dosages of 3.5mg/kg for 1 hour (approximately 250mg) and 1.5mg/kg for the next 2 hours (approximately 100mg), cephazolin produced a steady serum level at the third hour of approximately 28mcg/mL.

Table 2 shows the average serum concentrations after IV injection of a single 1g dose: average half-life was 1.4 hours.

Table 2 – Serum concentrations after 1g intravenous dose.

Serum Concentration (mcg/mL)					
5 min	15 min	30 min	1 Hr	2 Hr	4 Hr

188.4	135.8	106.8	73.7	45.6	16.5
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Controlled studies in adult normal volunteers receiving 1g 4 times a day for 10 days, monitoring CBC, AST, ALT, bilirubin, alkaline phosphatase, BUN, creatinine, and urinalysis indicated no clinically significant changes attributed to cefazolin.

Cefazolin is excreted unchanged in the urine primarily by glomerular filtration and, to a lesser degree, by tubular secretion. Following intramuscular injection of 500mg, 56% to 89% of the administered dose is recovered within 6 hours, and 80% to nearly 100% in 24 hours. Cephazolin achieves peak urine concentrations greater than 1000 mcg/mL and 4000 mcg/mL, respectively, following 500mg and 1g intramuscular doses.

In patients undergoing peritoneal dialysis (2L/hr) mean serum levels of cefazolin were approximately 10 and 30mcg/mL after 24 hours' instillation of a dialysing solution containing 50mcg/mL and 150mcg/mL, respectively. Mean peak levels were 29mcg/mL (range 13-44mcg/mL) with 50mcg/mL (3 patients), and 72mcg/mL (range 26-142 mcg/mL) with 150mcg/mL (6 patients).

Intraperitoneal administration of cefazolin is usually well tolerated.

When cefazolin is administered to patients with unobstructed biliary tracts, high concentrations well above serum levels occur in the gall-bladder tissue and bile. In the presence of obstruction, however, concentration of the antibiotic is considerably lower in bile than the serum.

Cefazolin readily crosses an inflamed synovial membrane, and the concentration of the antibiotic achieved in the joint space is comparable to levels measured in the serum.

Cefazolin readily crosses the placental barrier into the cord blood and amniotic fluid. It is present in very low concentrations in the milk of nursing mothers.

Indications

ZEPILEN is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory Tract Infection:

Due to *S. pneumoniae*, *Klebsiella sp*, *H. influenzae*, *Staph, aureus* (including penicillinase-producing strains), and Group A β -haemolytic streptococci. Injectable penicillin G benzathine is considered to be the medicine of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever.

ZEPILEN is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of Cephazolin in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary Tract Infections:

Due to *E. coli*, *P. mirabilis*, *Klebsiella* sp., and some strains of *Enterobacter* and enterococci.

Skin and Soft-tissue Infections:

Due to *Staph. aureus* (including penicillinase-producing strains) and Group A Beta-haemolytic streptococci and other strains of streptococci.

Biliary Tract Infections:

Due to *E. coli*, various strains of streptococci, *P. mirabilis*, *Klebsiella* sp., and *Staph. aureus*.

Bone and Joint Infections:

Due to *Staph. aureus*.

Septicaemia:

Due to *S. pneumoniae*, *Staph. aureus* (penicillin-susceptible and penicillin-resistant), *P. mirabilis*, *E. coli*, and *Klebsiella* sp.

Endocarditis:

Due to *Staph. aureus* (penicillin-susceptible and penicillin-resistant) and Group A β -haemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to ZEPILEN.

Perioperative Prophylaxis:

The prophylactic administration of ZEPILEN preoperatively, intraoperatively, and postoperatively may reduce the incidence of certain post-operative infections in patients undergoing surgical procedures that are classified as contaminated or potentially contaminated (e.g. vaginal hysterectomy, or cholecystectomy in high-risk patients, such as those over 70 years of age who have acute cholecystitis, obstructive jaundice, or common bile-duct stones).

The perioperative use of ZEPILEN may also be effective in surgical patients in whom infection at the operative site would present a serious risk (e.g. during open-heart surgery and prosthetic arthroplasty).

The prophylactic administration of ZEPILEN should usually be discontinued within a 24 hour period after the surgical procedure. For surgery in which the occurrence of infection may be particularly devastating (e.g. open-heart surgery and prosthetic arthroplasty), the prophylactic administration of ZEPILEN may be continued for 3 to 5 days following the completion of surgery. If there are signs of infection, specimens for cultures should be obtained for the identification of the causative organism so that appropriate therapy may be instituted. (See Dosage and Administration)

Dosage and Administration

ZEPILEN may be administered intramuscularly or intravenously after reconstitution. Total daily dosages are the same for either route of administration.

The intrathecal administration of ZEPILEN is not an approved route of administration for this antibiotic; in fact, there have been reports of severe CNS toxicity including seizures when ZEPILEN was administered in this manner.

Intramuscular Administration:

Reconstitute as directed in Table 3. Shake well until dissolved. The 500mg vial can be reconstituted with 0.9% Sodium Chloride Injection, Sterile Water for Injection or Bacteriostatic Water for Injection. The 1g vial should only be reconstituted with Sterile Water for Injection or Bacteriostatic Water for Injection.

ZEPILEN should be injected into a large muscle mass. Pain on injection is infrequent with ZEPILEN.

Table 3 – Dilution Table

Vial Size	Diluent to be Added	Approx. Available Volume	Approx. Average Concentration
500mg	2 mL	2.2 mL	225 mg/mL
1g*	2.5 mL	3 mL	330 mg/mL

Intravenous Administration:

ZEPILEN may be administered by intravenous injection or by continuous or intermittent infusion.

Intermittent Intravenous Infusion:

ZEPILEN may be administered along with primary intravenous fluid management programmes in a volume control set or in a separate, secondary IV bottle. Reconstituted 500mg or 1g of ZEPILEN may be diluted in 50 to 100mL of one of the following intravenous solutions: 0.9% Sodium Chloride Injection, 5% or 10% Dextrose Injection, 5% Dextrose in Lactated Ringer's Injection, 5% Dextrose and 0.9% Sodium Chloride Injection (also may be used with 5% Dextrose and 0.45% or 0.2% Sodium Chloride Injection), Lactated Ringer's Injection, 5% or 10% Invert Sugar in Sterile Water for Injection, Ringer's Injection, Normosol-M in D5-W, Ionosol B with Dextrose 5% or Plasma-Lyte with 5% Dextrose.

Intravenous Injection:

Administer solution directly into vein or through tubing. Dilute the reconstituted 500mg or 1g of ZEPILEN in a minimum of 10mL of Sterile Water for Injection. Inject solution slowly over a period of 3 to 5 minutes. Do not inject in less than 3 minutes.

Dosage:

The usual adult dosages are given in Table 4. In rare instances, doses up to 12g of ZEPILEN per day been used.

Table 4 – Usual Adult Dosage

Type of Infection	Dose	Frequency
Pneumococcal pneumonia	500mg	12 hourly
Mild infections caused by susceptible gram-positive cocci	250-500mg	8 hourly
Acute uncomplicated urinary tract infections	1g	12 hourly
Moderate to severe infections	500mg-1g	6-8 hourly
Severe, life threatening infections (e.g. endocarditis and septicaemia)*	1g-1.5g	6 hourly

Dosage adjustment for Patients with Reduced Renal Function:

ZEPILLEN may be used in patients with reduced renal function with the following dosage adjustments: Patients with a creatinine clearance ≥ 55 mL/min or a serum creatinine ≤ 1.5 mg% can be given full doses. Patients with creatinine clearance rates of 35 to 54 mL/min or serum creatinine of 1.6 to 3.0 mg % can also be given full doses but dosage should be restricted to at least 8-hour intervals. Patients with creatinine clearance rates of 11 to 34 mL/min or serum creatinine of 3.1 to 4.5 mg % should be given half the usual dose every 12 hours. Patients with creatinine clearance rates ≤ 10 mL/min or serum creatinine ≥ 4.6 mg % should be given one half the usual dose every 18 to 24 hours. All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection. For information about peritoneal dialysis, see Pharmacokinetics.

Perioperative Prophylactic Use:

To prevent postoperative infection in contaminated or potentially contaminated surgery, the recommended doses are as follows:

- 1g IV or IM administered 30 minutes to 1 hour prior to the start of surgery;
- For lengthy operative procedures (e.g. 2 hours or longer), 0.5 to 1g IV or IM during surgery (administration modified according to the duration of the operative procedure);
- 0.5 to 1g IV or IM every 6 to 8 hours for 24 hours postoperatively.

It is important that:

- The preoperative dose be given just prior (one half to 1 hour) to the start of surgery so that adequate antibiotic levels are present in the serum and tissues at the time of the initial surgical incision and
- If exposure to infections organisms is likely, ZEPILLEN be administered at appropriate intervals during surgery in order that sufficient levels of the antibiotic be present when needed.

In surgery in which infection may be particularly devastating (e.g. open heart surgery and prosthetic arthroplasty), the prophylactic administration of ZEPILLEN may be continued for 3 to 5 days following the completion of surgery.

Children:

In children, a total daily dosage of 25 to 50 mg/kg of body weight, divided into 3 or 4 equal doses, is effective for most mild to moderately severe infections (Table 5). Total daily dosage may be increased to 100 mg/kg of body weight for severe infections.

Table 5 – Paediatric dosage guide

Weight	25mg/kg day Divided into 3 doses		25mg/kg/day Divided into 4 doses	
Kg	Approx. single dose (mg 8 hourly)	Vol (mL) needed with dilution of 125mg/mL	Approx. single dose (mg 6 hourly)	Vol (mL) needed with dilution of 125mg/mL
4.5	40mg	0.35mL	30mg	0.25mL
9	75mg	0.6mL	55mg	0.45mL
13.6	115mg	0.9mL	85mg	0.7mL
18.1	150mg	1.2mL	115mg	0.9mL
22.7	190mg	1.5mL	140mg	1.1mL
Weight	50mg/kg day Divided into 3 doses		25mg/kg/day Divided into 4 doses	
kg	Approx. single dose (mg 8 hourly)	Vol (mL) needed with dilution of 225mg/mL	Approx. single dose (mg 6 hourly)	Vol (mL) needed with dilution of 225mg/mL
4.5	75mg	0.35mL	55mg	0.25mL
9	150mg	0.7mL	110mg	0.5mL
13.6	225mg	1mL	170mg	0.75mL
18.1	300mg	1.35mL	225mg	1mL
22.7	375mg	1.7mL	285mg	1.25mL

In children with mild to moderate renal impairment (creatinine clearance of 70 to 40 mL/min), 60% of the normal daily dose given in divided doses every 12 hours should be sufficient. In children with moderate impairment (creatinine clearance of 40 to 20mL/min), 25% of the normal daily dose given in divided doses every 12 hours should be sufficient. In children with severe impairment (creatinine clearance of 20 to 5mL/min), 10% of the normal daily dose given every 24 hours should be adequate. All dosage recommendations apply after an initial loading dose is administered.

Since safety for use in premature infants and in infants under 1 month of age has not been established, the use of ZEPILEN in these patients is not recommended.

Intraperitoneal administration:

Intraperitoneal administration of cefazolin is usually well tolerated.

Contraindications

ZEPILEN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings and Precautions

Warnings

Before ZEPILEN therapy is instituted, careful inquiry should be made concerning previous hypersensitivity reactions to cephalosporins and penicillin. Cephalosporin C derivatives should be given cautiously to penicillin-sensitive patients. Serious acute hypersensitivity reactions may require adrenaline and other emergency measures.

There is some clinical and laboratory evidence of partial cross-allergenicity between the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both medicines.

Antibiotics, including ZEPILEN should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to medicines.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhoea in association with the use of antibiotics. Such colitis may range in severity from mild to life threatening. In moderate to severe cases, appropriate measures should be taken.

Usage in Infants:

Safety for use in premature infants and infants under one month of age has not been established.

Precautions

General:

If an allergic reaction to ZEPILEN occurs, the medicine should be discontinued and the patient treated with the usual agents e.g. adrenaline or other pressor amines, antihistamines, or corticosteroids.

Prolonged use of ZEPILEN may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

When ZEPILEN is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see Dosage and Administration). The intrathecal administration of ZEPILEN is not an approved route of administration for this antibiotic; in fact, there have been reports of severe central nervous system (CNS) toxicity including seizures when cefazolin was administered in this manner.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of ZEPILEN have not been performed.

Use during Pregnancy and Lactation

Category B1

Reproduction studies have been performed in rats given doses of 500mg or 1g of ZEPILEN/kg and have revealed no evidence of impaired fertility or harm to the foetus due to ZEPILEN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this medicine should be used during pregnancy only if clearly needed.

When ZEPILEN has been administered prior to caesarean section, medicine levels in cord blood have been approximately one-fourth to one-third of maternal medicine levels. The medicine appears to have no adverse effect on the foetus.

ZEPILEN is present in very low concentrations in the milk of nursing mothers. Caution should be exercised when ZEPILEN is administered to a nursing woman.

Effects on ability to drive and use machines

This medicine is presumed to be safe or unlikely to produce an effect.

Adverse Effects

The following reactions have been reported:

Hypersensitivity:

Medicine fever, skin rash, vulvar pruritus, eosinophilia, Stevens-Johnson syndrome and anaphylaxis

Blood:

Neutropenia, leucopenia, thrombocytopenia, thrombocythaemia and positive direct and indirect Coombs' tests have occurred.

Renal:

Transient rise in BUN levels has been observed without clinical evidence of renal impairment. Interstitial nephritis and other renal disorders have been reported rarely. Most patients experiencing these effects have been seriously ill and were receiving multiple medicine therapies. The role of ZEPILEN in the development of nephropathies has not been determined.

Hepatic:

Transient rise in AST, ALT, and alkaline phosphatase levels have been observed rarely. As with some penicillins and some other cephalosporins transient hepatitis and cholestatic jaundice have been reported rarely.

Gastrointestinal:

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely. Anorexia, diarrhoea and oral candidiasis (oral thrush) have been reported.

Other:

Pain on intramuscular injection, sometimes with induration, has occurred infrequently. Phlebitis at the site of injection has been noted. Other reactions have included genital and anal pruritus, genital moniliasis, and vaginitis.

Interactions

Used concurrently, probenecid may decrease renal tubular secretion of cephalosporins resulting in increased and more prolonged cephalosporin blood levels.

A false-positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution, or CLINITEST Tablets, but not with enzyme-based tests, such as CLINISTIX and TES-TAPE.

Positive direct and indirect antiglobulin (Coombs') tests have occurred; these may also occur in neonates whose mothers received cephalosporins before delivery.

ZEPILLEN should not be mixed in the syringe with aminoglycoside antibiotics.

Overdosage

Symptoms

Toxic signs and symptoms following an overdose of Cephazolin may include pain, inflammation, and phlebitis at the injection site. The administration of inappropriately large doses of parenteral cephalosporins may cause dizziness, paresthesias, and headaches. Seizures may occur following overdosage with some cephalosporins, particularly in patients with renal impairment in whom accumulation is likely to occur.

Laboratory abnormalities that may occur after an overdose include elevations in creatinine, BUN, liver enzymes and bilirubin, a positive Coombs' test, thrombocytosis, thrombocytopenia, eosinophilia, leukopenia, and prolongation of the prothrombin time.

Treatment

In managing overdosage, consider the possibility of multiple medicine overdoses, interaction between medicines, and unusual medicine kinetics in your patient.

If seizures occur, the medicine should be discontinued promptly; anticonvulsant therapy may be administered if clinically indicated. Protect the patient's airway and

support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc.

In cases of severe overdosage, especially in a patient with renal failure, combined haemodialysis and haemoperfusion may be considered if response to more conservative therapy fails. However, no data supporting such therapy are available.

Pharmaceutical Precautions

When stored below 25°C ZEPILIN has a shelf life of 36 months. For reconstitution and dilution of ZEPILIN refer to Dosage and Administration.

Stability:

In those situations in which the medicine and the diluent have been mixed, but not immediately administered to the patient, the admixture may be stored under the following conditions:

Reconstituted ZEPILIN diluted in Sterile Water for Injection, 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Bacteriostatic Water for Injection is stable for 12 hours at room temperature and for 24 hours if stored under refrigeration (2° to 8°C).

Solutions of ZEPILIN in 10% Dextrose Injection, 5% Dextrose in Lactated Ringer's Injection, 5% Dextrose and 0.9% Sodium Chloride Injection (also may be used with 5% Dextrose and 0.45% or 0.2% Sodium Chloride Injection), Lactated Ringer's Injection, 5% or 10% Invert Sugar in Sterile Water for Injection, Ringer's Injection, Normosol-M in D5-W, Ionosol-B with Dextrose 5%, or Plasma-Lyte with 5% Dextrose should be used within 12 hours after dilution if stored at room temperature or within 24 hours if stored under refrigeration (2° to 8°C). (Do not freeze ZEPILIN diluted with the above diluents).

To reduce microbiological hazards, use as soon as practicable after reconstitution. ZEPILIN does not contain any anti-microbial agents and is intended for single use in one patient only. Discard any residue. Prior to administration, parenteral medicine products should be inspected visually for particulate matter and discolouration whenever solution and container permit.

Medicines Classification

Prescription medicine

Package Quantities

500mg and 1g: Packs of 10 vials

Further Information

The pH of the reconstituted solution is between 4.5 and 6. Each gram of cefazolin sodium contains 48.3 mg of sodium.

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Date of Preparation

19 September 2006