Product Monograph

PrZINACEF® for Injection

(sterile cefuroxime sodium USP)

Therapeutic Classification

Antibiotic

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Antibiotic

Action and Clinical Pharmacology

In vitro studies demonstrate that the bactericidal action of cefuroxime results from inhibition of bacterial cell wall synthesis by inhibiting the transpeptidase and carboxypeptidase enzymes.

Indications and Clinical Use

Treatment

ZINACEF® (sterile cefuroxime sodium) may be indicated for the treatment of patients with infections caused by susceptible strains of designated organisms in the following diseases:

Lower Respiratory Tract Infections

Pneumonia caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* including ampicillin-resistant strains, *Klebsiella* species, *Staphylococcus aureus* including ampicillin-resistant (but not methicillin-resistant) strains, *Streptococcus pyogenes*, and *Escherichia coli*.

Urinary tract Infections

Caused by *Escherichia coli* and *Klebsiella* species.

Soft Tissue Infections

Caused by *Staphylococcus aureus* including ampicillin-resistant (but not methicillin-resistant) strains, *Streptococcus pyogenes, Escherichia coli, Klebsiella* species.

Meningitis

Caused by *Staphylococcus aureus* including ampicillin-resistant (but not methicillin-resistant) strains, *Streptococcus pneumoniae, Haemophilus influenzae* and *Neisseria meningitidis*.

Gonorrhoea

Caused by *Neisseria gonorrhoea* including ampicillin-resistant strains.

Bone and Joint Infections

Caused by *Staphylococcus aureus* (penicillinase and non-penicillinase producing strains).

Specimens for bacteriologic culture should be obtained prior to therapy in order to identify the causative organisms and to determine their susceptibility to ZINACEF®. Therapy may be instituted before results of susceptibility testing are known. However, modification of the treatment may be required once these results become available.

Prevention

The pre-operative prophylactic administration of ZINACEF® may prevent the growth of susceptible disease-causing bacteria and thereby may reduce the incidence of certain post-operative infections:

- in patients undergoing surgical procedures (eg. vaginal hysterectomy) that are classified as clean contaminated or potentially contaminated;
- in patients undergoing open heart surgery in whom infections at the operative site would present a serious risk.

If signs of infection occur post-operatively, specimens for culture should be obtained for identification of the causative organism and appropriate anti-microbial therapy should be instituted.

Contraindications

ZINACEF® (sterile cefuroxime sodium) is contraindicated for patients who have shown Type 1 hypersensitivity to cefuroxime or to the cephalosporin group of antibiotics.

Warnings

Before therapy with ZINACEF® (sterile cefuroxime sodium) is instituted, careful enquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefuroxime, cephalosporins, penicillins, or other drugs. ZINACEF® should be administered with caution to any patient who has demonstrated some form of allergy, particularly to penicillins or other beta-lactams. There is some clinical and laboratory evidence of partial cross-allergenicity of the cephalosporins and penicillins.

If an allergic reaction to ZINACEF® occurs, treatment should be discontinued and standard agents (eg. epinephrine, antihistamines, corticosteroids) administered as necessary.

Pseudomembranous colitis has been reported to be associated with treatment of ZINACEF® (and other broad-spectrum antibiotics). Therefore, it is important to consider

its diagnosis in patients administered ZINACEF® who develop diarrhoea. Treatment with broad-spectrum antibiotics, including ZINACEF®, alters the normal flora of the colon and may permit overgrowth of Clostridia. Studies indicate that a toxin produced by *Clostridia difficile* is one primary cause of antibiotic-associated colitis. Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by discontinuance of ZINACEF® administration or when it is severe, consideration should be given to the administration of vancomycin or other suitable therapy. Other possible causes of colitis should also be considered.

Precautions

ZINACEF® (sterile cefuroxime sodium) should be administered with caution to individuals with a history of gastrointestinal disease, particularly colitis.

Patients with markedly impaired renal function (ie. creatinine clearance of 20 mL/min/1.73m^2 or less) should be placed on the special dosage schedule for ZINACEF® recommended under DOSAGE AND ADMINISTRATION. Normal dosages in these individuals are likely to produce excessive serum concentrations of cefuroxime.

Cephalosporin antibiotics at high dosage should be given with caution to patients receiving concurrent treatment with potent diuretics such as frusemide or aminoglycosides, as renal impairment has been reported with these combinations. Renal function should be monitored in these patients, the elderly, and those with pre-existing renal impairment (see DOSAGE and ADMINISTRATION).

The concomitant administration of aminoglycosides and some cephalosporins has caused nephrotoxicity. Although transient elevations of BUN and serum creatinine have been observed in clinical studies, there is no evidence that ZINACEF®, when administered alone, is significantly nephrotoxic.

Studies suggest that the concurrent use of potent diuretics, such as furosemide and ethacrynic acid, may increase the risk of renal toxicity with cephalosporins.

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

As with other antibiotics, prolonged treatment with ZINACEF® may result in the overgrowth of non-susceptible organisms (e.g. *Candida, enterococci, Clostridium difficile*), including species originally sensitive to the drug. This may require interruption of treatment. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken. Should an organism become resistant during antibiotic therapy, another antibiotic should be substituted.

As with other therapeutic regimens used in the treatment of meningitis, hearing loss has been reported in a few paediatric patients treated with ZINACEF®. Persistence of positive CSF cultures of Haemophilus influenzae at 18-36 hours has been noted with ZINACEF®.

Pregnancy

The safety of ZINACEF® in pregnancy has not been established. The use of ZINACEF® in pregnant women requires that the likely benefit from the drug be weighed against the

possible risk to the mother and fetus. Animal studies have shown cefuroxime to affect bone calcification in the fetus and to show maternal toxicity in the rabbit.

Nursing Mothers

Cefuroxime is excreted in human milk in low concentrations (0.5 mg/L). The clinical significance of this is unknown, therefore, caution should be exercised when ZINACEF® is administered to a nursing mother.

Elderly Patients

The elimination of cefuroxime may be reduced due to impairment of renal function. See "DOSAGE AND ADMINISTRATION, Dosage in Patients with Impaired Renal Function".

Drug Laboratory Test Interactions

Cefuroxime may interfere with Benedict's and Fehling's tests for glycosuria depending on copper reduction but not with enzyme-based tests for glycosuria. It may cause false-negative reactions in the ferricyanide test, and thus it is recommended that either the glucose oxidase or hexokinase methods be used to determine blood/plasma glucose levels in patients receiving ZINACEF®. Cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

Adverse Reactions

The following reactions have been observed during treatment with ZINACEF® (sterile cefuroxime sodium):

Hypersensitivity

Rash, and eosinophilia. Anaphylaxis, urticaria, pruritus, interstitial nephritis, cutaneous vasculitis and drug fever have also been observed with cephalosporin therapy. As with

other cephalosporins, there have been rare reports of erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis (exanthematic necrolysis).

Local reactions

Injection site reactions may include pain and thrombophlebitis. Stiffness at the site of injections, and inflammatory reactions at the site of injection; some degree of pain after intramuscular injections when using water as diluent, has been observed.

Blood

Increased erythrocyte sedimentation rate and decreased haemoglobin, eosinophilia, leukopenia, neutropenia and thrombocytopenia. Cephalopsporins as a class tend to be absorbed onto the surface of red cell membranes and react with antibodies directed against the drug to produce a positive Coombs' test (which can interfere with the cross matching of blood) and very rarely hemolytic anemia.

Renal:

Elevations in serum creatine, elevations in blood urea nitrogen and decreased creatine clearance (see WARNINGS and PRECAUTIONS).

Hepatic

Transient increases in serum bilirubin, transaminases and alkaline phosphatase.

Others

Drowsiness, gastrointestinal disturbance, loose stools, pseudomembranous colitis, faint feeling, sweating, palpitations and *Candida intertrigo*.

Symptoms and Treatment of Overdosage

Overdosage of cephalosporins can cause cerebral irritation leading to convulsions. Other than general supportive treatment, no specific antidote is known. Excessive serum levels of cefuroxime can be reduced by dialysis. For treatment of hypersensitivity reactions, see WARNINGS.

Dosage and Administration

DOSAGE

ZINACEF® (sterile cefuroxime sodium) may be administered either intravenously or intramuscularly after reconstitution.

Treatment

Dosage and route of administration should be determined by severity of infection, susceptibility of the causative organism(s), and condition of the patient. The intravenous route is preferable for patients with severe or life-threatening infections.

The usual duration of treatment is 5 to 14 days. For β-hemolytic Streptococcal infections, therapy should be continued for at least 10 days.

Adults

For most infections, the usual recommended dosage is 750 mg every 8 hours (2.25 g/day), administered either intravenously or intramuscularly. For severe or life-threatening infections, and for Gram-negative infections of the lower respiratory tract, a dosage of 1.5 g i.v. every 8 hours (4.5 g/day) is recommended.

For treatment of bacterial meningitis a dosage of 3 g i.v. every 8 hours (9 g/day) should be employed.

Uncomplicated gonorrhoea in both males and females, should be treated with a single intramuscular dose of 1.5 g, in two equally divided injections (one in each buttock), accompanied by a single oral dose of 1 g probenecid.

For bone and joint infections, a dosage of 1.5 g i.v. every 8 hours (4.5 g/day) is recommended. In clinical trials, surgical intervention was performed when indicated as an adjunct to ZINACEF® therapy. A course of oral antibiotics was administered when appropriate following the completion of parenteral administration of ZINACEF®.

Infants and Children (1 month to 12 years)

The usual dosage range is 30 to 100 mg/kg/day in 3 or 4 equally divided doses. A dose of 60 mg/kg/day is appropriate for most infections.

In cases of bacterial meningitis[1], a dosage of 200 to 240 mg/kg/day i.v. in 3 or 4 equally divided doses should be employed.

For bone and joint infections, a dosage between 70 to 150 mg/kg/day administered intravenously every 8 hours is recommended. In clinical trials a course of oral antibiotics was administered to children following the completion of parenteral administration of ZINACEF®.

Doses in excess of the maximum adult dose should not be used in infants and children.

[1] *Delayed sterilization of cerebral spinal fluid has been reported in a few children treated with cefuroxime for bacterial meningitis. Hearing impairment has occasionally occurred as a complication of meningitis in children treated with cefuroxime. See PRECAUTIONS.*

Neonates (up to 1 month):

In the first few weeks of life, the serum half-life of cefuroxime can be 3 to 5 times that in adults. Infections in neonates should be treated with dosages in the range of 30 to 100 mg/kg/day in 2 or 3 equally divided doses.

For bacterial meningitis[1] a dosage of 100 mg/kg/day i.v. in 2 or 3 equally divided doses should be employed.

Prevention

Clean contaminated or potentially contaminated surgical procedures

The recommended dose is 1.5 g of ZINACEF® administered intravenously just prior to surgery.

This may be supplemented with 750 mg administered intramuscularly or intravenously at 8 and 16 hours when surgery is prolonged.

In general, prophylactic administration is usually not required after the end of surgical procedures, however, intra-operative administrations should be considered if the surgical procedure is lengthy.

In many surgical procedures, continuing prophylactic administration of any antibiotic does not appear to be associated with a reduced incidence of subsequent infection, but will increase the possibility of adverse reactions and the development of bacterial resistance.

Open Heart Surgery

The recommended dosage is 1.5 g of ZINACEF® administered intravenously at the induction of anesthesia and every 12 hours thereafter for 48 hours.

Dosage in Patients with Impaired Renal Function

For patients with markedly impaired renal function a reduced dosage of ZINACEF® must be employed. For adult patients with moderate infections, dosage adjustment may be made according to the guidelines listed in TABLE 1.

TABLE 1: Dosage Adjustment For Adults With Renal Insufficiency

Creatinine Clearance		Unit Dose	Dosing Frequency
mL/min/1.73 m^2	mL/s/1.73 m^2		
> 20	> 0.33	750 mg - 1.5 g	q8h
10-20	0.17-0.33	750 mg	q12h
< 10	< 0.17	750 mg	q24h

For adults with severe infections who require doses higher than those recommended in TABLE 1, serum levels of cefuroxime should be monitored and dosage adjusted accordingly.

Studies in children with renal impairment are not sufficient to recommend specific dosages. If it is necessary to administer ZINACEF® to a child with such impairment, consideration should be given to modifying the frequency of drug administration consistent with the recommendations for adults with renal impairment as indicated in TABLE 1.

When only serum creatinine levels are known, the following formulae may be used to estimate creatinine clearance. The serum creatinine must represent a steady state of renal function.

Males :

$$\text{creatinine clearance (mL/min)} = \frac{\text{weight (kg) x (140-age)}}{\text{72 x serum creatinine (mg/dL)}}$$

OR

$$\text{creatinine clearance (mL/s)} = \frac{\text{weight (kg) x (140-age)}}{\text{49 x serum creatinine (µmol/L)}}$$

Females :

0.85 x male value.

For patients or haemodialysis, a further 750 mg dose of ZINACEF® should be administered at the end of each dialysis treatment.

ADMINISTRATION

Intramuscular

ZINACEF® should be injected into a large muscle mass to minimize pain. As the preparation is in suspension form, a 21-gauge needle should be used.

Intravenous

ZINACEF® may be administered intravenously either by a bolus injection or by a short intravenous infusion over a period of approximately 30 minutes.

For continuous intravenous infusions, a solution of ZINACEF® (1.5 g dissolved in 16 mL of Water for Injection) may be added to a suitable bottle containing an appropriate intravenous infusion fluid in the amount calculated to give the desired antibiotic dose.

Pharmaceutical Information

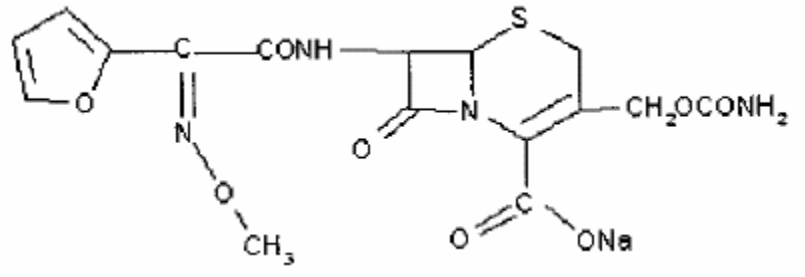
Chemistry

Trade Name: ZINACEF®

Proper Name: Sterile cefuroxime sodium

Chemical Name: 5-Thia-1-azabicyclo [4.2.0] oct-2-ene-2 carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[2-furanyl (methoxy-imino) acetyl]amino-8-oxo-,monosodium salt [6R-[6α, 7β (Z)]]

Structural Formula:



Molecular Formula: $C_{16}H_{15}N_4NaO_8S$

Molecular Weight: 446.4

Description: Cefuroxime sodium is white to faintly yellow crystalline powder, soluble in water (15% w/v at 25°C), sparingly soluble in ethanol and insoluble in chloroform, toluene, ether, ethyl acetate and acetone.

Composition

ZINACEF® vials contain cefuroxime sodium (expressed in terms of free acid). Freshly prepared solutions of cefuroxime are yellowish in colour, with some variations in intensity. The pH of freshly reconstituted solutions ranges from 6.0 to 8.5.

Reconstitution

For Intramuscular Use :

Reconstitute with Sterile Water for Injection.

Reconstitution Table

Vial Size	Diluent to be added to Vial	Volume to be Withdrawn	Approximate Cefuroxime Concentration
750 mg	3.0 mL	Total	220 mg/mL

Shake gently to produce an opaque suspension.

For Intravenous Use :

Reconstitute with Sterile Water for Injection.

Reconstitution Table

Vial Size	Diluent to be added to Vial	Volume to be Withdrawn	Approximate Cefuroxime Concentration
750 mg	8.0 mL	Total	90 mg/mL
1.5 g	16 mL	Total	90 mg/mL

Shake well until dissolved.

The reconstituted solution may be further diluted with Sodium Chloride Injection BP 0.9% w/v, 5% w/v dextrose Injection BP or Compound Sodium Lactate Injection BP (Hartmann's Solution). For short intravenous infusion, 1.5 g of ZINACEF® (sterile cefuroxime sodium) is dissolved in 49 mL Sterile Water for Injection, resulting in an approximate volume of 50 mL i.e. 30 mg/mL.

7.5g Pharmacy Bulk Vial

THE AVAILABILITY OF THE PHARMACY BULK VIAL IS RESTRICTED TO HOSPITAL WITH A RECOGNIZED INTRAVENOUS ADMIXTURE PROGRAM.

ZINACEF® FOR INJECTION does not contain any preservatives. The Pharmacy Bulk Vial is intended for multiple dispensing for intravenous use only, employing a single puncture. Reconstitute with 77 mL Sterile Water for Injection.

Reconstitution Table

Vial Size	Diluent to be added to Vial	Volume to be Withdrawn	Approximate Cefuroxime Concentration
7.5 g	77 mL	Amount needed*	95 mg/mL

*8 mL of solution contains 750mg of cefuroxime; 16mL of solution contains 1.5g of cefuroxime.

Shake well until dissolved.

Following reconstitution with Sterile Water for Injection, the solution should be dispensed for further dilution within eight hours. Any unused portion of the reconstituted solution should be discarded.

STABILITY OF SOLUTIONS

Storage

Reconstituted suspension for intramuscular injection and reconstituted solution for intravenous injection should be used within 6 hours if kept below 25°C or 48 hours if stored under refrigeration.

The further diluted solutions for intravenous infusion should be used within 12 hours if kept below 25°C or 36 hours if stored under refrigeration in the dark. Some increase in colour intensity may occur on storage.

NOTE : The pH of 2.74% w/v Sodium Bicarbonate Injection BP considerably affects the colour of the solution, therefore, this solution is not recommended for the dilution of ZINACEF® (sterile cefuroxime sodium). However, if required, for patients receiving Sodium Bicarbonate Injection by infusion, the ZINACEF® dose may be introduced into the tube of the set.

Incompatibility

ZINACEF® should not be mixed in the syringe with aminoglycoside antibiotics (e.g. gentamicin sulfate, tobramycin sulfate, amikacin sulfate) because of potential interaction.

Dosage Forms

Availability

ZINACEF® (sterile cefuroxime sodium) is available for intramuscular or direct intravenous injection in 17 mL vials containing cefuroxime sodium powder equivalent to 750 mg of cefuroxime in packs of ten.

For intravenous injection, 26 mL vials contain cefuroxime sodium powder equivalent to 1.5 g of cefuroxime, in packs of ten.

Pharmacy Bulk vial

For intravenous infusion, ZINACEF® is available in 127 mL vials containing cefuroxime sodium powder equivalent to 7.5 g of cefuroxime, in packs of six.

Storage

ZINACEF® in the dry state should be stored below 25°C and protected from light.

Microbiology

Cefuroxime has been shown to be active against the following organisms *in vitro:*

Gram-positive: *Streptococcus pyogenes, S. viridans* and *S. pneumoniae.* (Most strains of *Streptococcus faecalis* are resistant). *Staphylococcus aureus*, both penicillin-sensitive and beta-lactamase producing. (Some strains of methicillin-resistant *Staphylococci* have been found to be resistant to cefuroxime). *Clostridia.*

Gram-negative : *Escherichia coli* (including beta-lactamase-producing strains), *Klebsiella, Enterobacter, Haemophilus influenzae, Proteus mirabilis, Salmonella, Shigella spp., Neisseria gonorrhoeae* and *N. meningitidis.*

The following organisms are not susceptible to cefuroxime :

Clostridium difficile, Pseudomonas spp, Campylobacter spp, Acinetobacter calcoacetius, Listeria monocytogenes, Methicillin resistant strains of *Staphylococcus aureus*. Methicillin resistant strains of *Staphylococcus epidermidis* and *Legionella* spp. Some strains of the following genera are not susceptible to cefuroxime: *Streptococcus faecalis, Morganella morganii, Proteus vulgaris, Enterobacter* spp, *Citrobacter* spp, *Serratia* spp and *Bacteroides fragilis*.

The minimum inhibitory concentration against various organisms are shown in TABLES 2, 3 and 4.

TABLE 2: *In vitro* activity of cefuroxime against Gram-positive bacteria

Organism	No of strains	Inoculum size (CFU/ml)	Cumulative % of strains sensitive at indicated concentrations (μg/ml)										
			< 0.005	0.01	0.03	0.06	0.12	0.25	0.5	1.0	2.0	4.0	> 4.0
Staphylococcus aureus													
penicillin-sensitive	12	10^3							58	100			
penicillin-resistant	28	10^3							14	68	100		
methicillin-resistant	40	10^3							5	25	33		
coagulase-negative	39	10^3				3	10	28	54	79	85		
alpha- and non-haemolytic *Streptococci*	20	10^3	15	35	55	70	75	85	100				
beta-haemolytic *Streptococci*	40	10^3	8	50	80	95	98	100					
Streptococcus pneumoniae	19	10^3	53	100									
Clostridium spp.	7	10^3				13		26			86		100

TABLE 3: *In vitro* activity of cefuroxime against Gram-negative bacteria

Organism	No of strains	Inoculum size (CFU/ml)	Cumulative % of strains sensitive at indicated concentrations (μg/mL)					
			< 0.125	0.25-0.5	1-4	8-16	32-62	> 125
E coli	129	10^5		5	89	98	100	100
Klebsiella spp.	73	10^5			51	81	99	100
Acinetobacter	6	10^5		17	67	83	100	
Enterobacter spp.	138	10^5			22	88	94	100
Serratia spp.	8	10^5				13	25	75
Proteus mirabilis	27	10^5			89	96	100	
Proteus rettgeri	4	10^5	25			50	75	100
Proteus vulgaris	21	10^5				29	86	100
Morganella morganii	9	10^5			11	44	78	100
Salmonella spp.	40	10^5			95	98	100	
Shingles spp.	10	10^5			90		100	
B.fragilis	16	10^5			6	31	100	
H.influenzae								
ampicillin-sensitive	16	10^5		100				
ampicillin-resistant	15	10^5		100				

TABLE 4: *In vitro* activity of cefuroxime against gonococci

Organism	No of strains	Inoculum size (CFU/ml)	Cumulative % of strains sensitive at indicated concentrations (μg/mL)			
			< 0.03	0.06-0.25	0.5-2.0	> 2.0
N. gonorrhoea						
beta-lactamase positive	110	10^3	72	94	100	
beta-lactamase negative	752	10^3	60	92	97	100

Although cefuroxime is resistant to hydrolysis by most beta-lactamases, these enzymes from certain species (*Bacteroides fragilis, Enterobacter* and idole-positive *Proteus* spp) have been shown to cause hydrolysis. TABLE 5 shows the degree of resistance of cefuroxime to beta-lactamase inactivation.

TABLE 5: Hydrolysis of cefuroxime by a range of beta-lactamases

Source of enzyme	ENZYME Class	µg of cefuroxime hydrolyzed/minute
Escherichia coli (R^+ tem)	III	< 1
E. coli (R^+GN238)	V	4.5
E. coli D31	I	< 1
Proteus mirabilis	III	< 1
Klebsiella aerogenes K1	IV	54
Enterobacter cloacae P99	I	< 1
Proteus vulgaris	I	< 1
Bacteroides fragilis 1600	I	112
Pseudomonas aeruginosa 1822	I	< 1
Bacillus cereus 659/H9		72
*Staphylococcus aureus PC1**		< 1

* Activity is expressed as micrograms hydrolyzed per hour. Mice, rats and rabbits were inoculated intraperitoneally with a variety of Gram-positive and Gram- negative microbes such as *Staphylococcus aureus, E. coli, Proteus mirabilis, Klebsiella*). Cefuroxime, given intramuscularly, protected the animals against all of these test organisms at doses from 1 to 32 mg/kg. Doses of cefuroxime ranging from 35 to 133 mg/kg/dose were required for protection against infections from two strains of *Proteus vulgaris* and one strain of beta- lactamase- producing *E.coli*.

Susceptibility Testing

The result of susceptibility testing, by either disk-diffusion or tube-dilution techniques, should be interpreted according to the criteria in TABLE 6.

TABLE 6

	Zone diameter (30 µg cefuroxime disk)	Approximate MIC correlate
SUSCEPTIBLE (susceptible to the usual doses)	≥ 18 mm	≤ 8 µg/mL
INTERMEDIATE (moderately susceptible)*	15-17 mm	16 µg/mL
RESISTANT	≤ 14 mm	≥ 32 µg/mL
CONTROL STRAINS		
S.aureus ATCC 25923	27-35 mm	0.5-2 µg/mL
E.coli ATCC 25922	20-26 mm	2-8 µg/mL

* Organisms that produce zones of 15 to 17 mm may be susceptible if the infection is confined to tissues and fluids (e.g. urine) in which high antibiotic concentrations are attained.

Only cefuroxime disks should be used, since cefuroxime has been shown by *in vitro* tests to be active against certain strains found resistant when other beta-lactamase disks are used.

Pharmacology

ANIMAL

Cefuroxime, administered subcutaneously to mice at a dose of 4 g/kg, had no significant effect on the central nervous system, on spontaneous locomotor activity or motor co-ordination and no anticonvulsant, analgesic, tranquillizing or antidepressant properties. Intravenous administration of cefuroxime to cats and dogs at doses up to and including 300 mg/kg produced no pharmacodynamic effects on the cardiovascular or respiratory systems other than small variations in blood pressure and heart rate in the cat, which were not dose-related. However, doses of 1 and 3 g/kg produced an initial transitory tachycardia and a fall in blood pressure followed by bradycardia and an increase in blood pressure. In neither species did cefuroxime affect the responses of the cardiovascular system to intravenously-injected neurohumoral agents and ganglionic transmission was not affected in the cat.

Cefuroxime had no effect on isolated smooth muscle preparations at a concentration in the bathing fluid of 10^{-5} M. Only minor increases in contractile force and rate of contraction of the isolated rabbit heart (Langendorff preparation) were observed when the concentration in the perfusing fluid was increased to 10^{-2} M. Doses of 100 and 300 mg/kg administered intravenously to the cat had no effect on striated (voluntary) muscle activity, but small dose-related reductions in the muscle-twitch response were observed at doses of 1 and 3 g/kg. A 30% solution of cefuroxime in 0.9% saline had no local anaesthetic activity nor any irritant effect to the cornea of the rabbit eye.

Cefuroxime had no significant effect on the cortical EEG of rats.

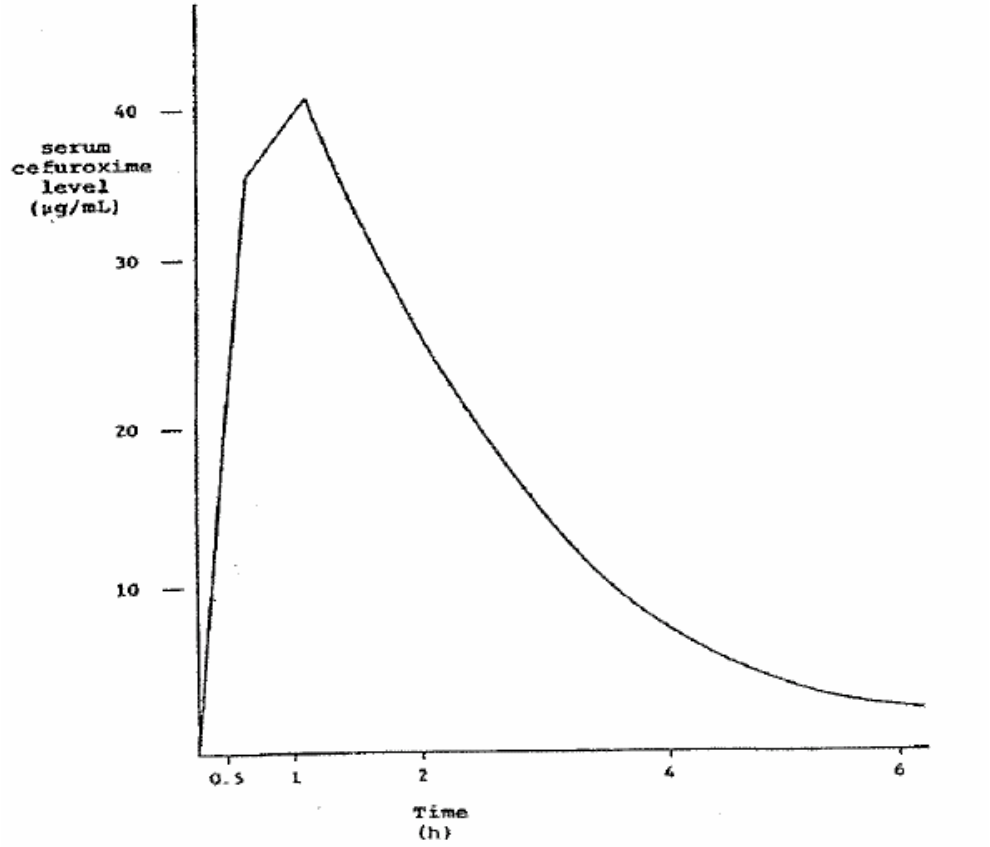
HUMAN

Cefuroxime is poorly absorbed when given orally; following a 1 g dose, serum levels of less than 1.2 µg/mL were observed and only between 1 and 1.3% of the administered dose was excreted in the urine. Cefuroxime, therefore, is used by the intramuscular or intravenous route.

Intramuscular Administration

Deep intramuscular injection of 750 mg of cefuroxime sodium in the lateral side of the thigh attained peak blood levels of 35 to 40 µg/mL after 30 to 40 minutes (FIGURE 1).

FIGURE 1: Serum cefuroxime levels following intramuscular injection of 750 mg



Serum cefuroxime concentrations greater than 12.5 µg/mL were maintained for approximately 3 hours, greater than 8 µg/mL for approximately 3.5 hours, and 6.25 µg/mL for approximately 4 hours, after a 750 mg dose administered intramuscularly.

About 90% of the administered dose was recovered in the urine within 6 hours of injection, and over 96% after 24 hours (TABLE 7).

TABLE 7: Mean urinary recoveries after parenteral cefuroxime

Route and dose (g)	Mean % urinary recovery at hours after injection							Total mean ± SD
	0-1	1-2	2-3	3-4	4-6	6-12	12-24	
IM								
0.25	26.4	31.6	17.7	9.3	6.4	4.0	0.4	95.8 ± 2.5
0.5	30.1	29.5	16.1	8.7	7.9	3.8	0.4	96.5 ± 7.9
0.75	35.6	29.3	17.3	9.0	6.9	3.6	0.2	101.9 ± 6.3
1.0	22.5	34.8	22.5	9.2	9.2	4.3	0.9	103.4 ±15.6
IV								
0.25	60.2	23.2	14.2	6.1	6.3	3.6	0.5	114.1 ± 6.1
0.5	41.3	23.6	13.1	6.9	5.6	4.0	0.6	95.1 ± 4.4
1.0	53.6	21.5	12.0	5.2	4.1	2.5	0.2	99.1 ± 0.2

Volume of distribution after a 750 mg dose was approximately 15 L (12.5 to 18.3 L) which increased to approximately 23 L when the dose of cefuroxime was doubled.

The mean half-life of a 750 mg intramuscular dose was approximately eighty minutes.

The effect of probenecid on the pharmacokinetics of cefuroxime is shown in TABLE 8.

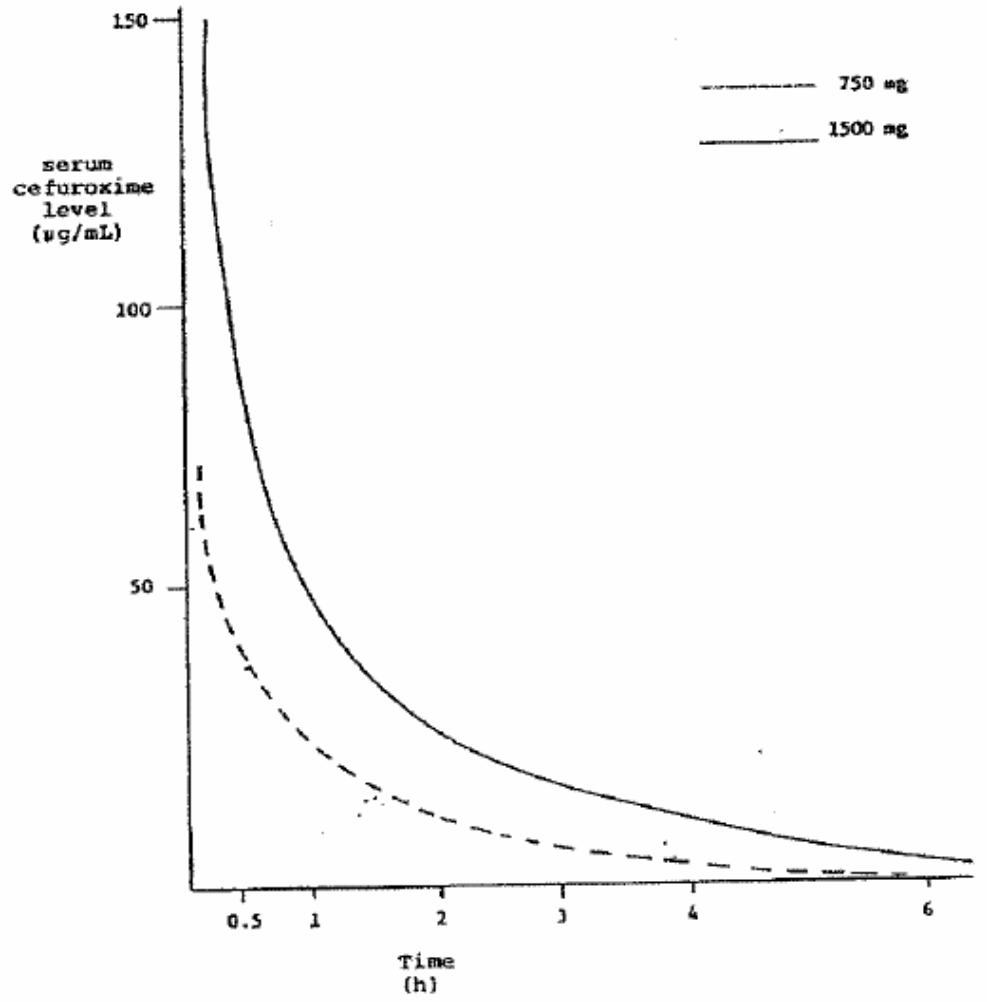
TABLE 8: Effect of probenecid (0.5 g given orally two hours before and one hour after cefuroxime) on the pharmacokinetics of intramuscular cefuroxime 500 mg

Pharmacokinetic variable	With probenecid	Without probenecid	Percentage change
Peak serum concentration (µg/mL)	29.4	22.7	+30
Ultimate serum half-life (min)	101	76.6	+32
Area under curve (µg/mL/h)	94.4	56.8	+56
Apparent volume of distribution (L/1.73m^2)	11.7	14.8	-20
Urinary recovery: 0-2h (%)	47	60.4	-22
0-24h	95.6	100.2	-5
Renal clearance (mL/min/1.73m^2)	79.6	133.8	-40
Cefuroxime/creatinine clearance ratio	0.74	1.25	-40

Intravenous Administration

Cefuroxime sodium 750 mg and 1.5 g resulted in blood levels of 73 µg/mL and 151 µg/mL, respectively (FIGURE 2), 5 minutes after the beginning of the injection.

FIGURE 2: Serum cefuroxime levels following intravenous injection



Intravenous infusion of 750 mg over a 30 minute period resulted in a serum level of 51 µg/mL at the end of the infusion. Intravenous administration of 1.5 g over a 20 minute period, resulted in a concentration of 146 µg/mL at the end of the infusion.

Following intravenous administration, more than 95% of cefuroxime was excreted unmetabolized via the kidneys (TABLE 5) with excretion evenly divided between glomerular filtration and tubular secretion. The half-life of cefuroxime after intravenous injection was approximately 65 minutes.

Patients With Renal Impairment

The effect of various degrees of renal impairment on the pharmacokinetics of cefuroxime is shown in TABLE 9.

TABLE 9: Pharmacokinetics of cefuroxime (750 mg) in patients with varying degrees of renal impairment

Patient No.	Mean Creatinine Clearance (mL/min)	Serum Concentration (µg/mL)		Serum Half-Life (h)	Urinary Concentrations (µg/mL)			
		peak	trough		0-2h	2-4h	4-6h	6-10h
1	21.0 (± 1.8)	101.0-62.4	9.2-8.0	4.3 (± 0.08)	150	177	145	135
2	23.0 (± 2.6)	80.3-72.6	9.7-8.0	4.2 (± 0.21)	180	225	102	85
3	12.1 - 17.8 (no mean available)	65.7-55.4	7.1-1.1	6.5 (± 0.37)	100	99	63	113
4	10.0 (± 1.4)	90.0-75.6	15.1-10.6	8.4 (± 0.41)	57	59	45	79
5	5.0 (± 2.0)	125.0-52.2	28.6-24.2	22.3 (± 2.03)	41	25	17	37

Fluid and Tissue Levels

Cefuroxime was detected in certain fluid and tissues as observed in TABLE 10.

TABLE 10: Concentrations of cefuroxime in different tissues

Site	Dose given (mg)	Route	Concentration (µg/mL)
Sputum	750 t.i.d. for 2 days	i.m.	2.0
	1500 t.i.d. for 4 days	i.m.	7.8
Bone	750 t.i.d. for 4 days	i.m.	3.9*
	1500 t.i.d. for 4 days	i.m.	13.5*
Skin blister	750 single	i.m.	9.4
Bile	750 single	i.m.	8.6
	1500 singe	i.m.	22.0
Aqueous Humour	1500 single	i.v.	1.6

* µg/g

An intravenous dose of 750 mg of cefuroxime resulted in biliary levels which varied considerably between 1.3 and 26 µg/mL. Biliary levels appear to be lowest in patients with a non-functioning gallbladder.

After a 750 mg intramuscular dose to 6 women in labour, average concentrations of cefuroxime in amniotic fluid (18.6 µg/mL) were similar to those in maternal serum; average peak maternal serum concentrations of 19.2 µg/mL were attained after 1.2 hours, while in umbilical cord blood, the average peaks were one third of those in the mothers.

Protein Binding

The extent of cefuroxime bound to protein in the serum was approximately 33%.

Toxicology

ACUTE TOXICITY

TABLE 11

Species	No. of animals	Dose (g/kg)	Route	Deaths
Mouse	10	11	i.v.	5
Rat	6	4	i.v.	3
Cat	4	2	i.m.	2
Monkey	4	2	i.m.	2
Dog	4	2	i.m.	2

Signs of toxicity immediately following i.v. administration in the rat included collapse and tachypnea. During the follow-up observation period (7 days), soft feces and a slight loss of body weight were observed in rats, while monkeys displayed diarrhea, accompanied by weight loss.

SUBACUTE TOXICITY

Rat

When rats were treated for a month with daily subcutaneous doses of 100 mg/kg of cefuroxime, the serum potassium was increased on day 34. With doses of 200 mg/kg/day, peripheral erythrocyte values were somewhat reduced in males and with 400 mg/kg/day in females. Daily doses of 800 mg/kg caused moderate reactions at the injection site forming subuctaneous lumps and occasionally ulcers. The ulcerations usually resolved within 10 days. There was also evidence of mild colitis. Rats were given doses of 1.25, 2.5 and 5.0 mg/kg/day of cefuroxime subcutaneously for 14 days. All of the animals showed signs of extreme discomfort during and immediately after injection. At autopsy, necrotic patches were observed at the injection sites of the rats given the highest dose. All rats had watery feces, increased leukocyte count, and a dose-related decrease in hemoglobin concentration.

One month treatment of rats with cefuroxime 50,100, 200 and 400 mg/kg/day intravenously, caused increased packed cell volume in all groups, increased urine output in the 200 mg/kg group and embolic reactions in many lungs, in both control and drug-treated animals. At doses of 100 and 400 mg/kg/day, a small but statistically significant decrease in spleen weights was observed.

Dog

Daily intramuscular administration of cefuroxime at doses of 60, 180 and 540 mg/kg for 11 days caused increased kidney and liver weights. In two male dogs, this was 1.5 times the weight of the controls.

Monkey

Cefuroxime administered intramuscularly for 29 days at doses of 150 and 450 mg/kg/day, caused a moderate decrease in erythrocytes, leukocytosis with neutrophilia, eosinophilia and soft stools.

In all subacute tests, there was a slight-to-moderate dose-related inflammatory reaction around the subcutaneous and intramuscular injection sites. Hemorrhage at the injection sites was sometimes observed, occurring more frequently at high doses.

CHRONIC TOXICITY

Rat : Three-month, subcutaneous study

Rats were dosed at 100, 300 and 900 mg/kg/day. A dose- and duration-related mild-to-marked subcutaneous reaction with haemorrhage at injection sites was observed at all 3 dose levels. Slight reduction of erythrocytes with mild reticulocytosis and slight reduction of serum calcium were observed at both 300 mg and 900 mg/kg dose levels. Increased prothrombin time was observed in males dosed at 300 mg/kg/day, and in both sexes at 900 mg/kg/day.

At 900 mg/kg/day an increased total leukocyte count, decreased serum albumin and gamma-globulin, increased serum potassium (females on day 56), marginally increased blood glucose (females on day 56) and decreased alkaline phosphatase (males on day 28) were observed. There was an increase in relative weights of the liver, the kidney and the spleen in all females. Increased excretion of electrolytes and increased urinary volume in both sexes were observed at the high dose level after 77 days.

Rat : Six-month subcutaneous study

Rats were observed at 50, 150 or 450 mg/kg/day. No mortality was observed. Dilatation of the lymphatics and enlargement of the spleen were observed at the higher doses. There was a statistically significant reduction of packed cell volume and haemoglobin, accompanied by reticulocytosis of a similar degree at 150 mg/kg/day. Reduction of serum alanine transaminase activity in both sexes as well as of pituitary weights in females were observed at the highest dose. Serum cholesterol was significantly increased in females at all dose levels while serum calcium levels were marginally reduced in males at high dose levels.

There was increased excretion of sodium and potassium, however, statistically significant changes were seen in the excretion of potassium in the high dose male animals only. Other abnormalities included hyaline granular casts and erythrocytes in the urine as well as increased urinary protein content. The incidence and severity of these changes were greatest at the high dose levels.

The mean kidney weights (absolute and relative) were increased 10 to 15% at high doses in both sexes.

Dog : Six-month toxicity study

Dogs received cefuroxime for 6 months at doses of 50 mg/kg/day intramuscularly, and doses of 150 and 450 mg/kg/day administered subcutaneously. There was a dose-related reaction at the injection site with subcutaneous haemorrhage occurring at the higher dose levels. In the group receiving the highest dose, hypochromia and increased serum iron binding capacity were observed. Serum triglyceride levels were increased after 20 weeks in animals receiving 150 and 450 mg/kg cefuroxime. Blood urea nitrogen was reduced and serum potassium was increased in the high dosage group. One dog in

the 450 mg group developed Heinz body anaemia after 12 weeks, but no causative agent was identified.

NEPHROTOXICITY STUDIES

Mouse

Mice received single subcutaneous doses of cefuroxime (10 g/kg) alone or in combination with furosemide (50 mg/kg) or furosemide plus glycerol (5.4 mL/kg). Cefuroxime alone caused no nephrotoxicity; together with furosemide there was proximal tubular necrosis in two out of nine animals. The combination of furosemide and glycerol caused tubular necrosis in 5 of 8 animals but this was not influenced by the addition of cefuroxime.

Rat : Single dose study

Cefuroxime at doses up to 10 g/kg was given either alone or together with furosemide (100 mg/kg) or furosemide plus glycerol (3.15 mL/kg). Three of 6 animals had proximal tubular necrosis in the inner cortex with 4 g of cefuroxime alone and the incidence and severity increased with increasing doses. The incidence of tubular necrosis also increased with increasing doses. The incidence of tubular necrosis also increased when furosemide or furosemide plus glycerol were given concomitantly. Cefuroxime at 1 g/kg enhanced the severity of the furosemide-glycerol-induced necrosis in the outer cortex. Treatment with furosemide plus glycerol also lowered the dosage of cefuroxime (to 2 g/kg) required to produce necrosis of the inner cortex.

Rat : Repeated dose study

Rats received cefuroxime at doses ranging from 1 to 5 g/kg/day subcutaneously for 10 days. There was no histological evidence of tubular necrosis at 5 g/kg, but transient increases in urine volume, protein and enzymes, which peaked at day 2-3 were

observed. The body weights of the animals were significantly reduced for the high dose group.

Combination with animoglycosides

Rats were treated with gentamicin (35 mg/kg) for 10 days. Cefuroxime was given either concomitantly during the 10 days or as a single dose with the ninth dose of gentamicin. Gentamicin-induced tubular necrosis was not potentiated by the administration of single doses of cefuroxime up to 6 g/kg/day. Multiple doses of cefuroxime up to 4 g/kg protected rats against gentamicin-induced nephrotoxicity, but at doses of 6 g/kg/day of cefuroxime, severe tubular necrosis was observed after 4 days of treatment. Similar results were found with amikacin and tobramycin.

TERATOGENICITY STUDIES

Mouse

Cefuroxime was administered subcutaneously at doses of 800, 1600, 3200 and 6400 mg/kg/day from day 6 to day 15 of pregnancy. At all doses, except at 3200 mg, there was a 15 to 21% incidence of bone immaturity as evidenced by a decrease in the calcification of various ossification centre, of the offspring. Based on historical controls, the untreated animals had a 7% incidence of bone immaturity.

Rabbit

Cefuroxime was administered intramuscularly at doses of 50, 100, 200 and 400 mg/kg/day from day 6 to day 18 or pregnancy. Four rabbits given 400 mg/kg, one rabbit given 200 mg/kg and one rabbit given 100 mg/kg/day, died during the test. The offspring had an 8, 17, 25 and 10% incidence of bone immaturity and the incidence of bone abnormalities was 8, 21, 0 and 30% at the 50, 100, 200 and 400 mg/kg dose levels, respectively.

Fertility and Reproduction Studies

Male and female mice were given daily subcutaneous doses of 800, 1600 or 3200 mg/kg of cefuroxime prior to mating (males for 60 days and females for 14 days). The pregnant females were continued on treatment until the 17th day of pregnancy. A few of their offspring were later mated to produce a second generation. Treatment had no apparent effect on gametogenesis. The fertility of the second generation was also unimpaired.

PERINATAL AND POSTNATAL STUDIES

Mouse

Daily subcutaneous doses of 800, 1600 and 3200 mg/kg of cefuroxime from day 16 of pregnancy until the weaning of the litters, had no effect on gestation, parturition, lactation or the health of the dams or the pups.

Rabbit

Daily administration of 50, 100 or 200 mg/kg of cefuroxime from day 19 of pregnancy through lactation (at least 50 doses) had no effect on the litters or the development and health of the pups. Treatment caused the death of 10 rabbits before parturition and one died after it had littered. Mortality was dose-related, and although believed to be caused by enteritis, a direct toxic effect could not be ruled out.

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