AF:LXX

PRESCRIBING INFORMATION

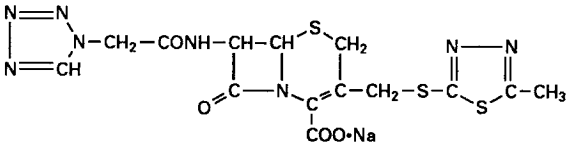
ANCEF®

cefazolin for injection

DESCRIPTION

Ancef (cefazolin for injection) is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3-{[(5-methyl-1,3,4-thiadiazol-2-yl)thio]-methyl}-8-oxo-7-[2-(1H-tetrazol-1-yl) acetamido]-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid.

Structural Formula:



Each vial contains 48 mg of sodium/1 gram of cefazolin sodium.

Ancef in lyophilized form is supplied in vials equivalent to 1 gram of cefazolin; in "Piggyback" Vials for intravenous admixture equivalent to 1 gram of cefazolin; and in Pharmacy Bulk Vials equivalent to 10 grams of cefazolin.

CLINICAL PHARMACOLOGY

Human Pharmacology: After intramuscular administration of *Ancef* to normal volunteers, the mean serum concentrations were 37 mcg/mL at 1 hour and 3 mcg/mL at 8 hours following a 500 mg dose, and 64 mcg/mL at 1 hour and 7 mcg/mL at 8 hours following a 1 gram dose.

Studies have shown that following intravenous administration of *Ancef* to normal volunteers, mean serum concentrations peaked at approximately 185 mcg/mL and were approximately 4 mcg/mL at 8 hours for a 1 gram dose.

The serum half-life for *Ancef* is approximately 1.8 hours following I.V. administration and approximately 2.0 hours following I.M. administration.

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

Studies in patients hospitalized with infections indicate that Ancef (cefazolin for injection) produces mean peak serum levels approximately equivalent to those seen in normal volunteers.

Bile levels in patients without obstructive biliary disease can reach or exceed serum levels by up to five times; however, in patients with obstructive biliary disease, bile levels of *Ancef* are considerably lower than serum levels (< 1.0 mcg/mL).

In synovial fluid, the *Ancef* level becomes comparable to that reached in serum at about 4 hours after drug administration.

Studies of cord blood show prompt transfer of *Ancef* across the placenta. *Ancef* is present in very low concentrations in the milk of nursing mothers.

Ancef is excreted unchanged in the urine. In the first 6 hours approximately 60% of the drug is excreted in the urine and this increases to 70% to 80% within 24 hours. *Ancef* achieves peak urine concentrations of approximately 2400 mcg/mL and 4000 mcg/mL respectively following 500 mg and 1 gram intramuscular doses.

In patients undergoing peritoneal dialysis (2 l/hr.), *Ancef* produced mean serum levels of approximately 10 and 30 mcg/mL after 24 hours' instillation of a dialyzing solution containing 50 mg/l and 150 mg/l, respectively. Mean peak levels were 29 mcg/mL (range 13-44 mcg/mL) with 50 mg/l (three patients), and 72 mcg/mL (range 26-142 mcg/mL) with 150 mg/l (six patients). Intraperitoneal administration of *Ancef* is usually well tolerated.

Controlled studies on adult normal volunteers, receiving 1 gram 4 times a day for 10 days, monitoring CBC, SGOT, SGPT, bilirubin, alkaline phosphatase, BUN, creatinine and urinalysis, indicated no clinically significant changes attributed to *Ancef*.

Microbiology: *In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. Ancef (cefazolin for injection) 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 cefazolin

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant)

Streptococcus pneumoniae
Escherichia coli
Proteus mirabilis
Klebsiella species
Enterobacter aerogenes
Haemophilus influenzae

Most strains of indole positive Proteus (*Proteus vulgaris*), *Enterobacter cloacae, Morganella morganii* and *Providencia rettgeri* are resistant. *Serratia, Pseudomonas, Mima, Herellea* species are almost uniformly resistant to cefazolin.

Disk Susceptibility Tests: ***Disk diffusion technique:*** Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure[1] has been recommended for use with disks to test susceptibility to cefazolin.

Reports from a laboratory using the standardized single-disk susceptibility test[1] with a 30 mcg cefazolin disk should be interpreted according to the following criteria:

Susceptible organisms produce zones of 18 mm or greater, indicating that the tested organism is likely to respond to therapy.

Organisms of intermediate susceptibility produce zones 15 to 17 mm, indicating that the tested organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids (e.g., urine), in which high antibiotic levels are attained.

Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be selected.

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

Gram-negative organisms should be tested with the cefazolin disk (using the above criteria), since cefazolin has been shown by *in vitro* tests to have activity against certain strains of *Enterobacteriaceae* found resistant when tested with the cephalothin disk. Gram-negative organisms having zones of less than 18 mm around the cephalothin disk may be susceptible to cefazolin.

Standardized procedures require use of control organisms. The 30 mcg cefazolin disk should give zone diameter between 23 and 29 mm for *E. coli* ATCC 25922 and between 29 and 35 mm for *S. aureus* ATCC 25923.

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

Dilution techniques: A bacterial isolate may be considered susceptible if the minimal inhibitory concentration (MIC) for cefazolin is not more than 16 mcg per mL. Organisms are considered resistant if the MIC is equal to or greater than 64 mcg per mL.

The range of MIC's for the control strains are as follows:

S. aureus ATCC 25923, 0.25 to 1.0 mcg/mL
E. coli ATCC 25922, 1.0 to 4.0 mcg/mL

INDICATIONS AND USAGE

Ancef (cefazolin for injection) is indicated in the treatment of the following serious infections due to susceptible organisms:

RESPIRATORY TRACT INFECTIONS due to *Streptococcus pneumoniae, Klebsiella* species, *Haemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever.

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

URINARY TRACT INFECTIONS due to *Escherichia coli, Proteus mirabilis, Klebsiella* species and some strains of enterobacter and enterococci.

SKIN AND SKIN STRUCTURE INFECTIONS due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), group A beta-hemolytic streptococci and other strains of streptococci.

BILIARY TRACT INFECTIONS due to *Escherichia coli*, various strains of streptococci, *Proteus mirabilis, Klebsiella* species and *Staphylococcus aureus*.

BONE AND JOINT INFECTIONS due to *Staphylococcus aureus*.

GENITAL INFECTIONS (i.e., prostatitis, epididymitis) due to *Escherichia coli, Proteus mirabilis, Klebsiella* species and some strains of enterococci.

SEPTICEMIA due to Streptococcus pneumoniae, Staphylococcus aureus (penicillin-sensitive and penicillin-resistant), Proteus mirabilis, Escherichia coli and Klebsiella species.

ENDOCARDITIS due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci.

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

PERIOPERATIVE PROPHYLAXIS: The prophylactic administration of *Ancef* preoperatively, intraoperatively and postoperatively may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures which are classified as contaminated or potentially contaminated (e.g., vaginal hysterectomy, and cholecystectomy in high-risk patients such as those over 70 years of age, with acute cholecystitis, obstructive jaundice or common duct bile stones).
The perioperative use of *Ancef* 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 *Ancef* should usually be discontinued within a 24-hour period after the surgical procedure. In surgery where the occurrence of infection may be particularly

devastating (e.g., open-heart surgery and prosthetic arthroplasty), the prophylactic administration of *Ancef* 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.)

CONTRAINDICATIONS

ANCEF (CEFAZOLIN FOR INJECTION) IS CONTRAINDICATED IN PATIENTS WITH KNOWN ALLERGY TO THE CEPHALOSPORIN GROUP OF ANTIBIOTICS.

WARNINGS

BEFORE THERAPY WITH *ANCEF* IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFAZOLIN, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO *ANCEF* OCCURS, DISCONTINUE TREATMENT WITH THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, IV FLUIDS, IV ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefazolin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of “antibiotic-associated colitis.”

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an oral antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

General: Prolonged use of Ancef (cefazolin for injection) may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When *Ancef* is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see DOSAGE AND ADMINISTRATION).

As with other beta-lactam antibiotics, seizures may occur if inappropriately high doses are administered to patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Ancef, as with all cephalosporins, should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.

Drug Interactions: Probenecid may decrease renal tubular secretion of cephalosporins when used concurrently, resulting in increased and more prolonged cephalosporin blood levels.

Drug/Laboratory Test Interactions: A false positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution or with Clinitest® tablets, but not with enzyme-based tests such as Clinistix®.

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

Carcinogenesis/Mutagenesis: Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of Ancef (cefazolin for injection) have not been performed.

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in rats, mice and rabbits at doses up to 25 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Ancef*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: When cefazolin has been administered prior to caesarean section, drug levels in cord blood have been approximately one quarter to one third of maternal drug levels. The drug appears to have no adverse effect on the fetus.

Nursing Mothers: Ancef (cefazolin for injection) is present in very low concentrations in the milk of nursing mothers. Caution should be exercised when *Ancef* is administered to a nursing woman.

Pediatric Use: Safety and effectiveness for use in premature infants and neonates have not been established. See DOSAGE AND ADMINISTRATION for recommended dosage in pediatric patients over 1 month.

ADVERSE REACTIONS

The following reactions have been reported:

Gastrointestinal: Diarrhea, oral candidiasis (oral thrush), vomiting, nausea, stomach cramps, anorexia and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS). Nausea and vomiting have been reported rarely.

Allergic: Anaphylaxis, eosinophilia, itching, drug fever, skin rash, Stevens-Johnson syndrome.

Hematologic: Neutropenia, leukopenia, thrombocytopenia, thrombocythemia.

Hepatic: Transient rise in SGOT, SGPT and alkaline phosphatase levels has been observed. As with other cephalosporins, reports of hepatitis have been received.

Renal: As with other cephalosporins, reports of increased BUN and creatinine levels, as well as renal failure, have been received.

Local Reactions: Rare instances of phlebitis have been reported at site of injection. Pain at the site of injection after intramuscular administration has occurred infrequently. Some induration has occurred.

Other Reactions: Genital and anal pruritus (including vulvar pruritus, genital moniliasis and vaginitis).

DOSAGE AND ADMINISTRATION

Usual Adult Dosage

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

*In rare instances, doses of up to 12 grams of *Ancef* per day have been used.

Perioperative Prophylactic Use

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

a. 1 gram I.V. or I.M. administered $^1/_2$ hour to 1 hour prior to the start of surgery.

b. For lengthy operative procedures (e.g., 2 hours or more), 500 mg to 1 gram I.V. or I.M. during surgery (administration modified depending on the duration of the operative procedure).

c. 500 mg to 1 gram I.V. or I.M. every 6 to 8 hours for 24 hours postoperatively.

It is important that (1) the preoperative dose be given just ($^1/_2$ to 1 hour) prior to the start of surgery so that adequate antibiotic levels are present in the serum and tissues at the time of initial surgical incision; and (2) *Ancef* be administered, if necessary, at appropriate intervals during surgery to provide sufficient levels of the antibiotic at the anticipated moments of greatest exposure to infective organisms.

In surgery where the occurrence of infection may be particularly devastating (e.g., open-heart surgery and prosthetic arthroplasty), the prophylactic administration of Ancef (cefazolin for injection) may be continued for 3 to 5 days following the completion of surgery.

Dosage Adjustment for Patients with Reduced Renal Function

Ancef may be used in patients with reduced renal function with the following dosage adjustments: Patients with a creatinine clearance of 55 mL/min. or greater or a serum creatinine of 1.5 mg % or less 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 $^1/_2$ the usual dose every 12 hours. Patients with creatinine clearance rates of 10 mL/min. or less or serum creatinine of 4.6 mg % or greater should be given $^1/_2$ 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. Patients undergoing peritoneal dialysis: See Human Pharmacology.

Pediatric Dosage

In pediatric patients, a total daily dosage of 25 to 50 mg per kg (approximately 10 to 20 mg per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg per kg (45 mg per pound) of body weight for severe infections. Since safety for use in premature infants and in neonates has not been established, the use of Ancef (cefazolin for injection) in these patients is not recommended.

Pediatric Dosage Guide		
Weight	**25 mg/kg/Day Divided into 3 Doses**	**25 mg/kg/Day Divided into 4 Doses**

Lbs	Kg	Approximate Single Dose mg/q8h	Vol. (mL) needed with dilution of 125 mg/mL	Approximate Single Dose mg/q6h	Vol. (mL) needed with dilution of 125 mg/mL
10	4.5	40 mg	0.35 mL	30 mg	0.25 mL
20	9.0	75 mg	0.60 mL	55 mg	0.45 mL
30	13.6	115 mg	0.90 mL	85 mg	0.70 mL
40	18.1	150 mg	1.20 mL	115 mg	0.90 mL
50	22.7	190 mg	1.50 mL	140 mg	1.10 mL

Weight		**50 mg/kg/Day Divided into 3 Doses**		**50 mg/kg/Day Divided into 4 Doses**	
Lbs	Kg	Approximate Single Dose mg/q8h	Vol. (mL) needed with dilution of 225 mg/mL	Approximate Single Dose mg/q6h	Vol. (mL) needed with dilution of 225 mg/mL
10	4.5	75 mg	0.35 mL	55 mg	0.25 mL
20	9.0	150 mg	0.70 mL	110 mg	0.50 mL
30	13.6	225 mg	1.00 mL	170 mg	0.75 mL
40	18.1	300 mg	1.35 mL	225 mg	1.00 mL
50	22.7	375 mg	1.70 mL	285 mg	1.25 mL

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

RECONSTITUTION

Preparation of Parenteral Solution

Parenteral drug products should be SHAKEN WELL when reconstituted, and inspected visually for particulate matter prior to administration. If particulate matter is evident in reconstituted fluids, the drug solutions should be discarded.

When reconstituted or diluted according to the instructions below, Ancef (cefazolin for injection) is stable for 24 hours at room temperature or for 10 days if stored under refrigeration (5°C or 41°F). Reconstituted solutions may range in color from pale yellow to yellow without a change in potency.

Single-Dose Vials

For I.M. injection, I.V. direct (bolus) injection or I.V. infusion, reconstitute with Sterile Water for Injection according to the following table. SHAKE WELL.

Vial Size	Amount of Diluent	Approximate Concentration	Approximate Available Volume
1 gram	2.5 mL	330 mg/mL	3.0 mL

Pharmacy Bulk Vials

Add Sterile Water for Injection, Bacteriostatic Water for Injection or Sodium Chloride Injection according to the table below. SHAKE WELL. Use promptly. (Discard vial within 4 hours after initial entry.)

Vial Size	Amount of Diluent	Approximate Concentration	Approximate Available Volume
10 grams	45 mL	1 gram/5 mL	51 mL
	96 mL	1 gram/10 mL	102 mL

"Piggyback" Vials

Reconstitute with 50 to 100 mL of Sodium Chloride Injection or other I.V. solution listed under ADMINISTRATION. When adding diluent to vial, allow air to escape by using a small vent needle or by pumping the syringe. SHAKE WELL. Administer with primary I.V. fluids, as a single dose.

ADMINISTRATION

Intramuscular Administration: Reconstitute vials with Sterile Water for Injection according to the dilution table above. Shake well until dissolved. *Ancef* should be injected into a large muscle mass. Pain on injection is infrequent with *Ancef*.

Intravenous Administration: Direct (bolus) injection: Following reconstitution according to the above table, further dilute vials with approximately 5 mL Sterile Water for Injection. Inject the solution slowly over 3 to 5 minutes, directly or through tubing for patients receiving parenteral fluids (see list below).

Intermittent or continuous infusion: Dilute reconstituted *Ancef* in 50 to 100 mL of one of the following solutions:

Sodium Chloride Injection, USP

5% or 10% Dextrose Injection, USP
5% Dextrose in Lactated Ringer's Injection, USP
5% Dextrose and 0.9% Sodium Chloride Injection, USP
5% Dextrose and 0.45% Sodium Chloride Injection, USP
5% Dextrose and 0.2% Sodium Chloride Injection, USP
Lactated Ringer's Injection, USP
Invert Sugar 5% or 10% in Sterile Water for Injection
Ringer's Injection, USP
5% Sodium Bicarbonate Injection, USP

HOW SUPPLIED

Ancef (cefazolin for injection)

Each vial contains cefazolin sodium equivalent to 1 gram of cefazolin.
NDC 0007-3130-16 (package of 25 vials)

Each vial contains cefazolin sodium equivalent to 1 gram of cefazolin.
NDC 0007-3137-05 (package of 10 "piggyback" vials)

Each vial contains cefazolin sodium equivalent to 10 grams of cefazolin.
NDC 0007-3135-05 (package of 10 pharmacy bulk vials)

As with other cephalosporins, *Ancef* tends to darken depending on storage conditions; within the stated recommendations, however, product potency is not adversely affected.

Before reconstitution protect from light and store at Controlled Room Temperature 20° to 25°C (68° to 77°F).

REFERENCE

1. Bauer, A.W.; Kirby, W.M.M.; Sherris, J.C., and Turck, M.: Antibiotic Testing by a Standardized Single Disc Method, Am. J. Clin. Path. 45:493, 1966. Standardized Disc Susceptibility Test, Federal Register 39:19182-19184, 1974.

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