CEFUNEX 750 MG/ CEFUNEX FORTE® (cefuroxime for injection)

CLINICAL PHARMACOLOGY: After intramuscular (IM) injection of a 750-mg dose of cefuroxime to normal volunteers, the mean peak serum concentration was 27 mcg/mL. The peak occurred at approximately 45 minutes (range, 15 to 60 minutes). Following IV doses of 750 mg and 1.5 g, serum concentrations were approximately 50 and 100 mcg/mL, respectively, at 15 minutes. Therapeutic serum concentrations of approximately 2 mcg/mL or more were maintained for 5.3 hours and 8 hours or more, respectively. There was no evidence of accumulation of cefuroxime in the serum following IV administration of 1.5-g doses every 8 hours to normal volunteers. The serum half-life after either IM or IV injections is approximately 80 minutes.

Approximately 89% of a dose of cefuroxime is excreted by the kidneys over an 8-hour period, resulting in high urinary concentrations.

Following the IM administration of a 750-mg single dose, urinary concentrations averaged 1300 mcg/mL during the first 8 hours. Intravenous doses of 750 mg and 1.5 g produced urinary levels averaging 1150 and 2500 mcg/mL, respectively, during the first 8-hour period.

The concomitant oral administration of probenecid with cefuroxime slows tubular secretion, decreases renal clearance by approximately 40%, increases the peak serum level by approximately 30%, and increases the serum half-life by approximately 30%. Cefuroxime is detectable in therapeutic concentrations in pleural fluid, joint fluid, bile, sputum, bone, and aqueous humor.

Cefuroxime is detectable in therapeutic concentrations in cerebrospinal fluid (CSF) of adults and pediatric patients with meningitis. The following table shows the concentrations of cefuroxime achieved in cerebrospinal fluid during multiple dosing of patients with meningitis.

Table 1: Concentrations of Cefuroxime Achieved in Cerebrospinal Fluid During Multiple Dosing of Patients with Meningitis

Patients	Dose	Number of Patients	Mean (Range) CSF Cefuroxime Concentrations (mcg/mL) Achieved Within 8 Hours Post Dose
Pediatric patients (4 weeks to 6.5 years)	200 mg/kg/day, divided q 6 hours	5	6.6 (0.9-17.3)
Pediatric patients (7 months to 9 years)	200 to 230 mg/kg/day, divided q 8 hours	6	8.3 (<2-22.5)
Adults	1.5 grams q 8 hours	2	5.2 (2.7-8.9)
Adults	1.5 grams q 6 hours	10	6.0 (1.5-13.5)

Cefuroxime is approximately 50% bound to serum protein.

Microbiology: Cefuroxime has in vitro activity against a wide range of gram-positive and gram-negative organisms, and it is highly stable in the presence of beta-lactamases of certain gram-negative bacteria. The bactericidal action of cefuroxime results from inhibition of cell-wall synthesis.

Cefuroxime is usually active against the following organisms in vitro.

Aerobes, Gram-positive: Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, and Streptococcus pyogenes (and other streptococci).

NOTE: Most strains of enterococci, e.g., Enterococcus faecalis (formerly Streptococcus faecalis), are resistant to cefuroxime. Methicillin-resistant staphylococci and Listeria monocytogenes are resistant to cefuroxime.

Aerobes, Gram-negative: Citrobacter spp., Enterobacter spp., Escherichia coli, Haemophilus influenzae (including ampicillin-resistant strains), Haemophilus parainfluenzae, Klebsiella spp.

INDICATIONS AND USAGE: CEFUNEX is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

1. Lower Respiratory Tract Infections, including pneumonia, caused by Streptococcus pneumoniae, Haemophilus influenzae (including ampicillin-resistant strains), Klebsiella spp., Staphylococcus aureus (penicillinase- and non–penicillinase-producing strains), Streptococcus pyogenes, and Escherichia coli.

2. Urinary Tract Infections caused by Escherichia coli and Klebsiella spp.

3. Skin and Skin-Structure Infections caused by Staphylococcus aureus (penicillinase- and non– penicillinase-producing strains), Streptococcus pyogenes, Escherichia coli, Klebsiella spp., and Enterobacter spp.

4. Septicemia caused by Staphylococcus aureus (penicillinase- and non–penicillinase-producing strains), Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae (including ampicillin-resistant strains), and Klebsiella spp.

5. Meningitis caused by Streptococcus pneumoniae, Haemophilus influenzae (including ampicillin-resistant strains), Neisseria meningitidis, and Staphylococcus aureus (penicillinase- and non–penicillinase-producing strains).

6. Gonorrhea: Uncomplicated and disseminated gonococcal infections due to Neisseria gonorrhoeae (penicillinase- and non–penicillinase-producing strains) in both males and females.

7. Bone and Joint Infections caused by Staphylococcus aureus (penicillinase- and non– penicillinase-producing strains). Clinical microbiological studies in skin and skin-structure infections frequently reveal the growth of susceptible strains of both aerobic and anaerobic organisms. CEFUNEX has been used successfully in these mixed infections in which several organisms have been isolated. Appropriate cultures and susceptibility studies should be performed to determine the susceptibility of the causative organisms to CEFUNEX.

Therapy may be started while awaiting the results of these studies; however, once these results become available, the antibiotic treatment should be adjusted accordingly. In certain cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, CEFUNEX may be used concomitantly with an aminoglycoside (see PRECAUTIONS). The recommended doses of both antibiotics may be given depending on the severity of the infection and the patient's condition.

Prevention: The preoperative prophylactic administration of CEFUNEX may prevent the growth of susceptible disease-causing bacteria and thereby may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures (e.g., vaginal hysterectomy) that are classified as clean-contaminated or potentially contaminated procedures. Effective prophylactic use of antibiotics in surgery depends on the time of administration. CEFUNEX should usually be given one-half to 1 hour

CEFUNEX® (cefuroxime for injection) CEFUNEX® (cefuroxime injection) before the operation to allow sufficient time to achieve effective antibiotic concentrations in the wound tissues during the procedure. The dose should be repeated intraoperatively if the surgical procedure is lengthy.

Prophylactic administration is usually not required after the surgical procedure ends and should be stopped within 24 hours. In the majority of surgical procedures, continuing prophylactic administration of

any antibiotic does not reduce the incidence of subsequent infections but will increase the possibility of adverse reactions and the development of bacterial resistance.

The perioperative use of CEFUNEX has also been effective during open heart surgery for surgical patients in whom infections at the operative site would present a serious risk. For these patients it is recommended that therapy with CEFUNEX be continued for at least 48 hours after the surgical procedure ends. If an infection is present, specimens for culture should be obtained for the identification of the causative organism, and appropriate antimicrobial therapy should be instituted.

CONTRAINDICATIONS: CEFUNEX is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS: BEFORE THERAPY WITH CEFUNEX IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CEFUNEX OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefuroxime, 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

Pediatric Use: Safety and effectiveness in pediatric patients below 3 months of age have not been established. Accumulation of other members of the cephalosporin class in newborn infants (with resulting prolongation of drug half-life) has been reported.

Geriatric Use: Of the 1914 subjects who received cefuroxime in 24 clinical studies of CEFUNEX, 901 (47%) were 65 and over while 421 (22%) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater susceptibility of some older individuals to drug effects cannot be ruled out. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: CEFUNEX is generally well tolerated. The most common adverse effects have been local reactions following IV administration. Other adverse reactions have been encountered only rarely.

Local Reactions: Thrombophlebitis has occurred with IV administration in 1 in 60 patients.
Gastrointestinal: Gastrointestinal symptoms occurred in 1 in 150 patients and included diarrhea (1 in 220 patients) and nausea (1 in 440 patients). The onset of pseudomembranous colitis may occur during or after antibacterial treatment (see WARNINGS).

Hypersensitivity Reactions: Hypersensitivity reactions have been reported in fewer than 1% of the patients treated with CEFUNEX and include rash (1 in 125). Pruritus, urticaria, and positive Coombs' test each occurred in fewer than 1 in 250 patients, and, as with other cephalosporins, rare cases of anaphylaxis, drug fever, erythema multiforme, interstitial nephritis, toxic epidermal necrolysis, and Stevens-Johnson syndrome have occurred.

Blood: A decrease in hemoglobin and hematocrit has been observed in 1 in 10 patients and transient eosinophilia in 1 in 14 patients. Less common reactions seen were transient neutropenia (fewer than 1 in 100 patients) and leukopenia (1 in 750 patients). A similar pattern and incidence were seen with other cephalosporins used in controlled studies. As with other cephalosporins, there have been rare reports of thrombocytopenia.

Hepatic: Transient rise in SGOT and SGPT (1 in 25 patients), alkaline phosphatase (1 in 50 patients), LDH (1 in 75 patients), and bilirubin (1 in 500 patients) levels has been noted.

Kidney: Elevations in serum creatinine and/or blood urea nitrogen and a decreased creatinine clearance have been observed, but their relationship to cefuroxime is unknown.

Postmarketing Experience with CEFUNEX Products: In addition to the adverse events reported during clinical trials, the following events have been observed during clinical practice in patients treated with CEFUNEX and were reported spontaneously. Data are generally insufficient to allow an estimate of incidence or to establish causation.

Neurologic: Seizure.

Non-site specific: Angioedema.

Cephalosporin-class Adverse Reactions: In addition to the adverse reactions listed above that have been observed in patients treated with cefuroxime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Vomiting, abdominal pain, colitis, vaginitis including vaginal candidiasis, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage.

Several cephalosporins, including CEFUNEX, have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see DOSAGE AND ADMINISTRATION). If seizures associated with drug therapy should occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Altered Laboratory Tests: Prolonged prothrombin time, pancytopenia, agranulocytosis.

OVERDOSAGE: Overdosage of cephalosporins can cause cerebral irritation leading to convulsions. Serum levels of cefuroxime can be reduced by hemodialysis and peritoneal dialysis.

DOSAGE AND ADMINISTRATION:

Dosage: Adults: The usual adult dosage range for CEFUNEX is 750 mg to 1.5 grams every 8 hours, usually for 5 to 10 days. In uncomplicated urinary tract infections, skin and skin-structure infections, disseminated gonococcal infections, and uncomplicated pneumonia, a 750-mg dose every 8 hours is recommended. In severe or complicated infections, a 1.5-gram dose every 8 hours is recommended.

In bone and joint infections, a 1.5-gram dose every 8 hours is recommended. In clinical trials, surgical intervention was performed when indicated as an adjunct to therapy with CEFUNEX. A course of oral antibiotics was administered when appropriate following the completion of parenteral administration of CEFUNEX.

In life-threatening infections or infections due to less susceptible organisms, 1.5 grams every 6 hours may be required. In bacterial meningitis, the dosage should not exceed 3 grams every 8 hours. The recommended dosage for uncomplicated gonococcal infection is 1.5 grams given intramuscularly as a single dose at 2 different sites together with 1 gram of oral probenecid. For preventive use for clean-contaminated or potentially contaminated surgical procedures, a 1.5-gram dose administered intravenously just before surgery (approximately one-half to 1 hour before the initial incision) is recommended. Thereafter, give 750 mg intravenously or intramuscularly every 8 hours when the procedure is prolonged.

For preventive use during open heart surgery, a 1.5-gram dose administered intravenously at the induction of anesthesia and every 12 hours thereafter for a total of 6 grams is recommended.

Impaired Renal Function: A reduced dosage must be employed when renal function is impaired. Dosage should be determined by the degree of renal impairment and the susceptibility of the causative organism (see Table 2).

Table 2: Dosage of CEFUNEX in Adults With Reduced Renal Function.

Creatinine Clearance (mL/min)	Dose	Frequency
>20	750 mg-1.5 grams	q8h
10-20	750 mg	q12h
<10	750 mg	q24h*

* Since CEFUNEX is dialyzable, patients on hemodialysis should be given a further dose at the end of the dialysis.

When only serum creatinine is available, the following formula2 (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.