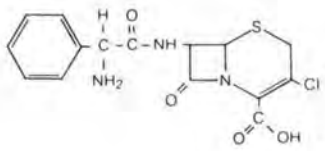
CECLOR®*

(cefaclor)

DESCRIPTION

CECLOR (cefaclor, USP, LILLY) is a semisynthetic cephalosporin antibiotic for oral administration. It is chemically designated as 3-chloro-7-D (2-phenyl-glycinamido)-3-cephem-4-carboxylic acid monohydrate.

Cefaclor has the following structural formula:



PRESENTATION▲

- CECLOR 500 mg: capsules, each equivalent to 500 mg (1.36 mmol) cefaclor.
- CECLOR 250 mg: capsules, each equivalent to 250 mg (0.68 mmol) cefaclor.

- CECLOR 125 mg: granules, to obtain 60 ml, 75 ml, or 100 ml suspensions respectively, equivalent to 125 mg (0.34 mmol) cefaclor per tea-spoon (= 5 ml).
- CECLOR 187 mg: granules, to obtain 50 ml or 100 ml suspensions respectively, equivalent to 187 mg (0.51 mmol) cefaclor per tea-spoon (= 5 ml).
- CECLOR 250 mg: granules, to obtain 60 ml, 75 ml, or 100 ml suspensions respectively, equivalent to 250 mg (0.68 mmol) cefaclor per tea-spoon (= 5 ml).
- CECLOR 375 mg: granules, to obtain 50 ml or 100 ml suspensions respectively, equivalent to 375 mg (1.0 mmol) cefaclor per tea-spoon (= 5 ml).

CLINICAL PHARMACOLOGY

Cefaclor is well absorbed after oral administration to fasting subjects. Total absorption is the same whether the drug is given with or without food, however, when it is taken with food, the peak concentration achieved is 50% to 75% of that observed when the drug is administered to fasting subjects and generally appears from 45 to 60 minutes later. Following administration of 250 mg, 500 mg, and 1 g doses to fasting subjects, average peak serum levels of approximately 7, 13, and 23 mg/l, respectively, were obtained within 30 to 60 minutes. Approximately 60% to 85% of the drug is excreted unchanged in the urine within 8 hours, the greater portion being excreted within the first 2 hours. During this 8 hour period, peak urine concentrations following the 250 mg, 500 mg, and 1 g doses were approximately 600, 900, and 1900 mg/l, respectively. The serum half-life in normal subjects is 0.6 to 0.9 hour. In patients with reduced renal function, the serum half-life of cefaclor is slightly prolonged. In those with complete absence of renal function, the plasma half-life of the intact molecule is 2.3 to 2.8 hours. Excretion pathways in patients with markedly impaired renal function have not been determined. Hemodialysis shortens the half-life by 25% to 30%.

Microbiology - *In vitro* tests demonstrate that the bactericidal action of the cephalosporins results from their inhibition of cell-wall synthesis. While *in vitro* studies have demonstrated the susceptibility of most strains of the following organisms to cefaclor, clinical efficacy for infections other than those included in the INDICATIONS section is unknown.

- *Aerobes, Gram-positive*:
  Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains (when tested by *in vitro* methods), exhibit cross-resistance between cefaclor and methicillin
  Streptococcus pneumoniae
  Streptococcus pyogenes

- *Aerobes, Gram-negative*:
  Citrobacter diversus
  Escherichia coli
  Haemophilus influenzae, including β-lactamase-producing, ampicillin-resistant strains
  Klebsiella spp.
  Moraxella (Branhamella) catarrhalis
  Neisseria gonorrhoeae
  Proteus mirabilis

- *Anaerobes*:
  Bacteroides spp. (excluding *Bacteroides fragilis*)
  Peptococcus niger
  Peptostreptococcus spp.
  Propionibacteria acnes

NOTE: Methicillin-resistant staphylococci and most strains of enterococci (*Enterococcus faecalis* [formerly *Streptococcus faecalis*] and *Enterococcus faecium* (formerly *Streptococcus faecium*)] are resistant to cefaclor and other cephalosporins. Cefaclor is not active against most strains of *Enterobacter* spp., *Serratia* spp., *Morganella morganii*, *Proteus vulgaris*, and *Providencia rettgeri*. It has no activity against *Pseudomonas* spp. or *Acinetobacter* spp.

Disc susceptibility tests

Diffusion techniques: Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility of bacteria to antimicrobial agents. One such standard procedure[1] has been recommended for use with discs to test susceptibility of organisms to CECLOR, using the 30 µg cefalotin disc. Interpretation involves the correlation of the diameters obtained in the disc test with the minimum inhibitory concentration (MIC) for cefaclor.

Reports from the laboratory giving results of the standard single-disc susceptibility test with a 30 µg cefalotin disc should be interpreted according to the following criteria:

Zone diameter (mm)	Interpretation
⩾18	(S) Susceptible
15-17	(MS) Moderately susceptible
⩽14	(R) Resistant

Although the spectrum of activity of cefaclor is qualitatively similar to that of cefalotin and of the other first-generation cephalosporins, its activity against *H. influenzae* is considerably greater than that of the first generation cephalosporins. For this reason, a disc containing 30 µg of cefaclor may be used to determine the susceptibility of *H. influenzae* using the method described by NCCLS. In the testing of *H. influenzae* (on Mueller-Hinton agar supplemented with hemoglobin and a commercial VX supplement) or other organisms, zone diameter interpretative criteria, are identical to those used for the cefalotin disc: ⩾18 mm, susceptible; 15-17 mm, moderately susceptible (intermediate for *Haemophilus*); and ⩽14 mm, resistant.

A report of "susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "moderately susceptible" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids in which high antibiotic levels are obtained. A report of "resistant" indicates that achievable concentration of the antibiotic are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 30 µg cefalotin disc should give the following zone diameters:

Organism	Zone diameter (mm)
E. coli ATCC 25922	15-21
S. aureus ATCC 25923	29-37

Dilution techniques: Use a standardized dilution method[2] (broth, agar, microdilution) or equivalent with cefaclor powder. The MIC values obtained should be interpreted according to the following criteria:

MIC (µg/ml)	Interpretation
⩽8	Susceptible
16	Moderately susceptible
⩾32	Resistant

As with standard diffusion techniques, dilution methods require the use of laboratory control organisms. Standard cefaclor powder should provide the following MIC values:

Organism	MIC (µg/ml)
S. aureus ATCC 29213	1-4
E. coli ATCC 25922	1-4
E. faecalis ATCC 29212	>32.0

INDICATIONS

CECLOR is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

- *Otitis media* - Caused by *S. pneumoniae*, *H. influenzae*, staphylococci, *S. pyogenes* (group A β-hemolytic streptococci), and *M. catarrhalis*
- *Lower respiratory tract infections* - Including pneumonia, caused by *S. pneumoniae*, *H. influenzae*, *S. pyogenes* (group A β-hemolytic streptococci), and *M. catarrhalis*
- *Upper respiratory tract infections* - Including pharyngitis and tonsillitis, caused by *S. pyogenes* (group A β-hemolytic streptococci), and *M. catarrhalis*.

NOTE: Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Amoxicillin has been recommended by the American Heart Association as the standard regimen for the prophylaxis of bacterial endocarditis for dental, oral, and upper respiratory tract procedures, with penicillin V a rational and acceptable alternative in the prophylaxis against α-hemolytic streptococcal bacteremia in this setting. Cefaclor is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of cefaclor in the subsequent prevention of either rheumatic fever or bacterial endocarditis are not available at present.

- *Urinary tract infections* - Including pyelonephritis and cystitis, caused by *E. coli*, *P. mirabilis*, *Klebsiella* spp., and coagulase-negative staphylococci.

NOTE: Cefaclor has been found to be effective in both acute and chronic urinary tract infections.

- *Skin and skin structure infections* - Caused by *Staphylococcus aureus* and *S. pyogenes* (group A β-hemolytic streptococci)
- *Sinusitis*
- *Gonococcal urethritis*

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

CONTRAINDICATION

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

WARNINGS

Before therapy with CECLOR is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefaclor, cephalosporins, penicillins, or other drugs. If this product is to be given to penicillin-sensitive patients, caution should be exercised because cross-hypersensitivity, including anaphylaxis, among β-lactam antibiotics has been clearly documented.

If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

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

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 diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening. Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, appropriate measures should be taken.

PRECAUTIONS

General - Prolonged use of cefaclor may result in the overgrowth of non susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. It should be recognized that a positive Coombs' test may be due to the drug, e.g., in hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition.

CECLOR should be administered with caution in the presence of markedly impaired renal function. Since the half-life of cefaclor in anuria is 2.3 to 2.8 hours, dosage adjustments for patients with moderate or severe renal impairment are usually not required. Clinical experience with cefaclor under such conditions is limited, therefore, careful clinical observation and laboratory studies should be made.

Antibiotics, including cephalosporins, should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Drug / Laboratory test interactions - Patients receiving cefaclor may show a false-positive reaction for glucose in the urine with tests that use Benedict's and Fehling's solutions and also with CLINITEST tablets but not with TES-TAPE* (Glucose Enzymatic Test Strip, USP, LILLY).

There have been rare reports of increased anticoagulant effect when cefaclor and oral anticoagulants were administered concomitantly (see ADVERSE REACTIONS). As with other β-lactam antibiotics, the renal excretion of cefaclor is inhibited by probenecid.

Carcinogenesis, mutagenesis, impairment of fertility - Studies have not been performed to determine potential for carcinogenicity or mutagenicity. Reproduction studies have revealed no evidence of impaired fertility.

Usage in pregnancy - Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given 3 times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to CECLOR. 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 - The effect of CECLOR on labor and delivery is unknown.

Nursing mothers - Small amounts of CECLOR have been detected in mother's milk following administration of single 500 mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mg/l at 2, 3, 4, and 5 hours respectively. Trace amounts were detected at 1 hour. The effect on nursing infants is not known. Caution should be exercised when CECLOR is administered to a nursing woman.

Pediatric use - Safety and effectiveness of this product for use in infants less than 1 month of age have not been established.

ADVERSE REACTIONS

Adverse effects considered to be related to therapy with CECLOR are listed below:

Hypersensitivity reactions have been reported in about 1.5% of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria and positive Coombs' tests each occur in less than 1 in 200 patients.

Cases of *serum-sickness-like* reactions have been reported with the use of cefaclor. These are characterized by findings of erythema multiforme, rashes, and other skin manifestations accompanied by arthritis/arthralgia, with or without fever, and differ from classic serum sickness in that there is infrequently associated lymphadenopathy and proteinuria, no circulating immune complexes, and no evidence to date of sequelae of the reaction. While further investigation is ongoing, *serum-sickness-like* reactions appear to be due to hypersensitivity and more often occur during or following a second (or subsequent) course of therapy with cefaclor. Such reactions have been reported more frequently in children than in adults with an overall occurrence ranging from 1 in 200 (0.5%) in one focused trial to 2 in 8,346 (0.024%) in overall clinical trials (with an incidence in children in clinical trials of 0.055%) to 1 in 38,000 (0.003%) in spontaneous event reports. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy; occasionally these reactions have resulted in hospitalization, usually of short duration (median hospitalization = 2 to 3 days, based on postmarketing surveillance studies). In those requiring hospitalization, the symptoms have ranged from mild to severe at the time of admission with more of the severe reactions occurring in children. Antihistamines and glucocorticoids appear to enhance resolution of the signs and symptoms. No serious sequelae have been reported.

More severe hypersensitivity reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and anaphylaxis have been reported rarely. Anaphylaxis may be more common in patients with a history of penicillin allergy.

Gastrointestinal symptoms occur in about 2.5% of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely. As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Other effects considered related to therapy included eosinophilia (1 in 50 patients), genital pruritus or vaginitis (less than 1 in 100 patients), and, rarely, thrombocytopenia or reversible interstitial nephritis.

Causal relationship uncertain -

CNS - Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, hallucinations, and somnolence have been reported.

Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic - Slight elevations of AST (SGOT), ALT (SGPT), or alkaline phosphatase values (1 in 40).

Hematopoietic - As has also been reported with other β-lactam antibiotics, transient lymphocytosis, leukopenia, and, rarely, hemolytic anemia, aplastic anemia, agranulocytosis, and reversible neutropenia of possible clinical significance.

There have been rare reports of increased prothrombin time with or without clinical bleeding in patients receiving cefaclor and coumadin concomitantly.

Renal - Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

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

OVERDOSAGE

Signs and symptoms - The toxic symptoms following an overdose of cefaclor may include nausea, vomiting, epigastric distress, and diarrhea. The severity of the epigastric distress and the diarrhea are dose related. If other symptoms are present, it is probable that they are secondary to an underlying disease state, an allergic reaction, or the effects of other intoxication.

Treatment - In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Unless 5 times the normal dose of CECLOR has been ingested, gastrointestinal decontamination will not be necessary.

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. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for an overdose of cefaclor.

DOSAGE AND ADMINISTRATION

CECLOR is administered orally.

Adults - The usual adult dosage is 250 mg every 8 hours. For bronchitis and pneumonia, the dosage is 250 mg administered 3 times daily. A dosage of 250 mg administered 3 times daily for 10 days is recommended for sinusitis. For more severe infections (such as pneumonia) or those caused by less susceptible organisms, doses may be doubled. Doses of 4 g/day have been administered safely to normal subjects for 28 days, but the total daily dosage should not exceed this amount.

For the treatment of acute gonococcal urethritis in males and females, a single dose of 3 g combined with probenecid, 1 g, is given.

Children - The usual recommended daily dosage for children is 20 mg/kg/day in divided doses every 8 hours. For bronchitis and pneumonia, the dosage is 20 mg/kg/day in divided doses administered 3 times daily.

In more serious infections, otitis media, and infections caused by less susceptible organisms, 40 mg/kg/day in divided doses are recommended, with a maximum dosage of 1 g/day.

Child's weight (kg)	CECLOR Suspension			
	20 mg/kg/day		40 mg/kg/day	
	125 mg/5 ml	250 mg/5 ml	125 mg/5 ml	250 mg/5 ml
9	1/2 tsp t.i.d.		1 tsp t.i.d.	1/2 tsp t.i.d.
18	1 tsp t.i.d.	1/2 tsp t.i.d.		1 tsp t.i.d.

B.I.D. Treatment option: for the treatment of otitis media and pharyngitis, the total daily dosage may be divided and administered every 12 hours.

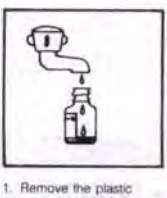
Child's weight (kg)	CECLOR Suspension			
	20 mg/kg/day (Pharyngitis)		40 mg/kg/day (Otitis media)	
	187 mg/5 ml	375 mg/5 ml	187 mg/5 ml	375 mg/5 ml
9	1/2 tsp b.i.d.		1 tsp b.i.d.	1/2 tsp b.i.d.
18	1 tsp b.i.d.	1/2 tsp b.i.d.		1 tsp b.i.d.

CECLOR may be administered in the presence of impaired renal function. Under such a condition, the dosage usually is unchanged (see PRECAUTIONS).

In the treatment of β-hemolytic streptococcal infections, a therapeutic dosage of CECLOR should be administered for at least 10 days.

Store at controlled room temperature, 15° to 30°C.

After mixing the oral suspension, store in a refrigerator. Keep tightly closed and shake well before using. The mixture may be kept for 14 days without significant loss of potency. Discard unused portion after 14 days.



1. Remove the plastic cup measure which is placed on bottle cap. Open bottle and add a small quantity of water at first to help mixing of powder.

2. Replace cap and shake.

3. Now add water again up to the level of the red arrow on side of label.

4. Shake well.

5. Pour out liquid into plastic cup measure. The mark on cup of 2.5 ml is equal to 1/2 teaspoonful. The mark of 5 ml = 1 teaspoonful.

6. Drink directly from plastic cup measure. After dosing wash out cup.