CECLOR® MR

CEFACLOR ADVANCED FORMULATION EXTENDED-RELEASE TABLETS

DESCRIPTION

Ceclor MR, Lilly, is a pharmaceutically-modified form of the orally active cephalosporin, cefaclor. It is a semisynthetic cephalosporin antibiotic for oral administration. The active ingredient is chemically designated as 3-chloro-7-D-(2-phenylglycinamido)-3-cephem-4-carboxylic acid monohydrate and is known as Cefaclor, USP. Ceclor MR differs from cefaclor in its rate of dissolution, producing a lower peak serum concentration, but retaining sustained measurable serum concentrations, which provides the advantage of twice daily dosing.
Each extended-release tablet contains cefaclor monohydrate equivalent to 375 mg (0.972 mmol), 500 mg (1.296 mmol), or 750 mg (1.944 mmol) cefaclor.

CLINICAL PHARMACOLOGY

Ceclor MR is well absorbed from the gastrointestinal tract after oral administration. Although Ceclor MR can be taken with or without food, total absorption is enhanced with food. When it was given within 1 hour after a meal, the bioavailability of Ceclor MR was greater than 90%, using cefaclor as a reference. When taken in the fasting state, the bioavailability of Ceclor MR was 77% that of cefaclor. Compared to cefaclor (fasted state), mean peak plasma concentrations of Ceclor MR (both fed and fasted states) were delayed 40 to 90 minutes and were lower. Concomitant administration of H_2 blockers does not affect the rate or extent of absorption. Administration of magnesium- or aluminum hydroxide-containing antacids 1 hour after Ceclor MR had no effect on the rate of absorption but resulted in a 17% decrease in the extent of absorption.
Following administration of 375-mg, 500-mg, and 750-mg tablets to fed subjects, average peak serum concentrations of 4, 8, and 11 µg/mL, respectively, were obtained within 2.5 to 3 hours. No drug accumulation was noted when it was given twice daily.
The plasma half-life in healthy subjects is independent of dosage form and averages approximately 1 hour (range 0.6 to 0.9). In elderly subjects (over age 65) with normal serum creatinine values, a higher peak plasma concentration and AUC are effects resulting from mildly diminished renal function and have no apparent clinical significance. Therefore, dosage changes are not necessary in elderly subjects with normal renal function. There is no evidence of metabolism of cefaclor in humans.
Microbiology--The in vitro bactericidal activity of Ceclor MR is due to cefaclor. In vitro tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell-wall synthesis. Cefaclor is stable in the presence of bacterial ß-lactamases; consequently, ß-lactamase-producing organisms resistant to penicillins and some cephalosporins may be susceptible to cefaclor. Ceclor MR has been shown to be active against most strains of the following organisms both in vitro and in clinical infections (see Indications and Usage):
Gram-positive organisms:
Staphylococcus aureus (including ß-lactamase-producing strains)
Staphylococcus epidermidis (including ß-lactamase-producing strains)
Staphylococcus saprophyticus
Streptococcus pneumoniae
Streptococcus pyogenes (group A streptococci)
NOTE: Cefaclor is inactive against methicillin-resistant staphylococci.
Gram-negative organisms:
Haemophilus parainfluenzae
Haemophilus influenzae (including ß-lactamase-producing strains)
Moraxella (Branhamella) catarrhalis (including ß-lactamase-producing strains)
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Cefaclor has been shown to be active in vitro against most strains of the following organisms; however, clinical efficacy has not been established:
Gram-negative organisms:
Citrobacter diversus
Neisseria gonorrhoeae
Anaerobic organisms:
Propionibacterium acnes
Bacteroides species (excluding Bacteroides fragilis)
Peptococci
Peptostreptococci
NOTE: *Pseudomonas* sp, *Acinetobacter calcoaceticus*, most strains of enterococci, *Enterobacter* sp, indole-positive *Proteus*, and *Serratia* sp are resistant to cefaclor.
Susceptibility Testing
Diffusion Techniques--Quantitative methods that require measurement of zone diameters give an estimate of antibiotic susceptibility. One such procedure is the National Committee for Clinical Laboratory Standards (NCCLS) approved procedure.[1] This method has been recommended for use with disks to test susceptibility to cefaclor. Interpretation involves correlation of the diameters obtained in the disk test with minimum inhibitory concentrations (MIC) for cefaclor. Reports from the laboratory giving results of the standard single-disk susceptibility test with a 30-µg cefaclor disk should be interpreted according to the following criteria:
Zone diameter (mm) Interpretation
≥ 18 (S) Susceptible
15-17 (I) Intermediate
≤ 14 (R) Resistant
When Testing* *H. influenzae*
Zone diameter (mm) Interpretation
≥ 20 (S) Susceptible
17-19 (I) Intermediate
≤ 16 (R) Resistant
*Disk susceptibility tests performed using Haemophilus Test Medium (HTM)

A report of "susceptible" implies that the pathogen is likely to be inhibited by generally achievable blood concentrations. A report of "intermediate" indicates that inhibitory concentrations of the antibiotic may be achieved if high dosage is used or if the infection is confined to tissues and fluids (eg, urine) in which high antibiotic concentrations are attained. A report of "resistant" indicates that achievable concentrations 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 cefaclor disk should give the following zone diameters:
Organism Zone Diameter (mm)
E. coli ATCC 25922 23-27
S. aureus ATCC 25923 27-31
H. influenzae ATCC 49766* 25-31
*Disk susceptibility tests performed using Haemophilus Test Medium (HTM)

Pathogens other than *M. catarrhalis* and *H. influenzae* can be tested using the 30-µg cephalothin disk or by a dilution test. Ceclor MR administration was associated with a favorable clinical and bacteriologic response in virtually all cases of infection from *M .catarrhalis*, regardless of zone diameter, thus there is little gained by testing cefaclor against this organism. *H. influenzae* should be tested with the cefaclor disk on chocolate Mueller-Hinton and interpreted by the usual zone diameter criteria depicted previously. Alternatively, *H. influenzae* may be tested on Haemophilus Test Medium (HTM) using the interpretive criteria recommended by NCCLS listed below:
Zone diameter (mm) Interpretation
≥ 24 (S) Susceptible
19-23 (I) Intermediate
≤ 18 (R) Resistant
Dilution Techniques--Broth and agar dilution methods, such as those recommended by the NCCLS,[2] may be used to determine the MIC of cefaclor. MIC test results should be interpreted according to the following criteria:
MIC (µg/mL) Interpretation
≤8 (S) Susceptible
16 (I) Intermediate
≥32 (R) Resistant
As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard cefaclor powder should give the following MIC values:
Organism MIC range (µg/mL)
E. coli ATCC 25922 1-4
S. aureus ATCC 29213 1-4
E. faecalis ATCC 29212 >32.0
H. influenzae ATCC 49766* 1-4
*Broth microdilution tests performed using Haemophilus Test Medium (HTM)

INDICATIONS AND USAGE

Ceclor MR is indicated in the treatment of the following infections when caused by susceptible strains of the designated organisms:
Acute bronchitis and acute exacerbations of chronic bronchitis caused by *S. pneumoniae, H. influenzae* (including ß-lactamase-producing strains), *H. parainfluenzae, M. catarrhalis* (including ß-lactamase-producing strains), and *S. aureus*.
Pharyngitis and tonsillitis caused by *S. pyogenes* (group A streptococci). (Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Ceclor MR is generally effective in the eradication of streptococci from the oropharynx; however, substantial data establishing the efficacy of Ceclor MR in the subsequent prevention of rheumatic fever are not available.)
Pneumonia caused by *S. pneumoniae, H. influenzae* (including ß-lactamase-producing strains), and *M. catarrhalis* (including ß-lactamase-producing strains).
Sinusitis caused by *S. pneumoniae* (penicillin susceptible strains only), *H. influenzae* (including ß-lactamase-producing strains), and *M. catarrhalis*(including ß-lactamase-producing strains).
Uncomplicated lower urinary tract infections, including cystitis and asymptomatic bacteriuria, caused by *E. coli, K. pneumoniae, P. mirabilis,* and *S. saprophyticus.*
Skin and skin structure infections caused by *S. pyogenes* (group A streptococci), *S. aureus* (including ß-lactamase-producing strains), and *S. epidermidis* (including ß-lactamase-producing strains).
Bacteriologic studies to determine the causative organism and its susceptibility to cefaclor should be performed. Therapy may be started while awaiting the results of these studies. Once these results become available, antimicrobial therapy should be adjusted accordingly.

CONTRAINDICATION

Ceclor MR is contraindicated in patients with known hypersensitivity to cefaclor and other cephalosporins.

WARNINGS

BEFORE THERAPY WITH Ceclor MR 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 Ceclor MR OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Antibiotics, including Ceclor MR, 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–The possibility of emergence of resistant organisms which might result in overgrowth should be kept in mind, particularly during prolonged treatment. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Drug Interactions–The extent of absorption of Ceclor MR is diminished if magnesium- or aluminum hydroxide-containing antacids are taken within 1 hour of administration of Ceclor MR. However, either the rate or the extent of absorption of Ceclor MR, as with other ß-lactam antibiotics, the renal excretion of cefaclor (and presumably Ceclor MR) is inhibited by probenecid. No other significant drug interactions were noted during clinical trials.

Laboratory Test Interactions–Administration of Ceclor MR may result in a false-positive reaction for glucose in the urine. This phenomenon has been seen in patients taking cephalosporin antibiotics when the test is performed using Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape®(Glucose Enzymatic Test Strip, USP, Lilly).

Carcinogenesis, Mutagenesis, Impairment of Fertility–Studies in animals have not been performed to evaluate the carcinogenic or mutagenic potential for Ceclor MR. 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 maximum human dose and in ferrets given 3 times the maximum human dose. These studies have revealed no evidence of impaired fertility or harm to the fetus due to cefaclor. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Ceclor MR should be used during pregnancy only if clearly needed.

Labor and Delivery–Ceclor MR has not been studied for use during labor and delivery. Treatment should be given only if clearly needed.

Nursing Mothers–No studies have been done with Ceclor MR. Small amounts of cefaclor have been detected in mother's milk following administration of single 500-mg doses of cefaclor. Average levels were 0.18, 0.20, 0.21, and 0.16 µg/mL 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 MR is administered to a nursing woman.

Pediatric Use–Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The majority of adverse reactions observed in clinical trials of Ceclor MR were mild and transient. Drug-related adverse reactions requiring discontinuation of therapy occurred in 1.7% of patients. The following adverse reactions have been reported following the use of Ceclor MR in clinical trials or since marketing and were less than 1 in 100 (less than 1%), except as otherwise noted.

Gastrointestinal: Diarrhea (3.4%), nausea (2.5%), vomiting, and dyspepsia.

Hypersensitivity: Rash, urticaria, or pruritus occurred in approximately 1.7% of patients. One **serum-sickness-like** reaction (0.03%) was reported among the 3,272 patients treated with Ceclor MR during the controlled clinical trials.

Cases of **serum-sickness-like** reactions have been reported with the use of cefaclor. These are characterized by findings of erythema multiforme, rashes, 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. Occasionally, solitary symptoms may occur, but do not represent a **serum-sickness-like** 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 literature review to 1 in 4,615 (0.022%) in a small clinical trial 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.

Hematologic and Lymphatic Systems: Eosinophilia.

Genitourinary: Vaginal moniliasis (2.5%) and vaginitis (1.7%).

The following adverse effects have been reported in patients treated with Ceclor MR; causal relationship is uncertain:

Central Nervous System: Headache, dizziness, and somnolence.

Hepatic: Transient elevations in AST, ALT, and alkaline phosphatase.

Renal: Transient increase in BUN or creatinine.

Laboratory Tests: Transient thrombocytopenia, leukopenia, lymphocytosis, neutropenia, and abnormal urinalysis.

In addition to the adverse reactions listed above that have been observed in patients taking Ceclor MR, the following adverse reactions and altered laboratory tests have been reported in patients treated with cefaclor:

Erythema multiforme, rare anaphylaxis (may be more common in patients with a history of penicillin allergy), Stevens-Johnson syndrome, positive direct Coombs' test, and genital pruritus. Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.

Anaphylactoid events may be manifested by solitary symptoms, including angioedema, asthenia, edema (including face and limbs), dyspnea, paresthesias, syncope, or vasodilatation.

Rarely, hypersensitivity symptoms may persist for several months.

The following reactions have been reported rarely in patients treated with cefaclor:

Toxic epidermal necrolysis, reversible interstitial nephritis, hepatic dysfunction including cholestasis, increased prothrombin time in patients receiving cefaclor and warfarin concomitantly, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, aplastic anemia, agranulocytosis, and hemolytic anemia.

In addition to the adverse reactions listed above, the following adverse reactions have been reported in patients treated with ß-lactam antibiotics: Colitis, renal dysfunction, and toxic nephropathy.

Several ß-lactam antibiotics have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. If seizures associated with drug therapy should 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 Ceclor MR 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. 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 MR may be given orally without regard to meals. However, absorption is enhanced when Ceclor MR is administered with food (*see* Clinical Pharmacology). The tablets should not be cut, crushed, or chewed.

The recommended dosage for pharyngitis and tonsillitis and skin and skin structure infections is 375 mg twice daily. For lower urinary tract infections, the recommended dosage is 375 mg twice daily or 500 mg once daily. The recommended dosage for bronchitis is 375 mg or 500 mg twice daily. For pneumonia and sinusitis the recommended dosage is 750 mg twice daily.

In the treatment of infections caused by *S. pyogenes* (group A streptococci), a therapeutic dosage of Ceclor MR should be administered for at least 10 days.

Ceclor MR should be stored at controlled room temperature, 15° to 30°C (59° to 86°F).

REFERENCES

1.National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial disk susceptibility tests - 5th ed., Approved Standard NCCLS Document M2-A5, Vol 13, No 24, NCCLS, Villanova, PA, 1993.

2.National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically - 3rd ed., Approved Standard NCCLS Document M7-A3, Vol 13, No 25, NCCLS, Villanova, PA, 1993.

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