CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 64-081

FINAL PRINTED LABELING

NDC 0332-3206-24

15 Capsules

CEFACLOR CAPSULES USP 250 mg

Lot #

Discard After

Keep tightly closed. Store at controlled room temperature 15°-30°C (59°-86°F).

Mfd. by: Biocraft Laboratories, Inc. Elmwood Park, NJ 07407 1193

SEP 16 1996

NDC 0332-3206-24

15 Capsules

CEFACLOR CAPSULES USP 250 mg

APPROVED

Each capsule contains cefaclor monohydrate equivalent to 250 mg cefaclor.

CAUTION: Federal (USA) law prohibits dispensing without prescription.

biocraft

Usual Adult Dosage: 250 mg three times a day. For severe infections, this dosage may be doubled. See accompanying literature.

N 3 0332-3206-24 2

100 Capsules NDC 0332-3206-09

CEFACLOR CAPSULES USP 250 mg

APPROVED

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biocraft

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Keep tightly closed.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container.

Mfd. by: Biocraft Laboratories, Inc. Elmwood Park, NJ 07407 1193

LOT

EXP SEP 16 1996

N 3 0332-3206-09 9

500 Capsules NDC 0332-3206-13

CEFACLOR CAPSULES USP 250 mg

APPROVED

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biocraft

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LOT

EXP SEP 16

N 3 0332-3206-13 6

CEFACLOR CAPSULES, USP

250 mg and 500 mg

DESCRIPTION

Cefaclor is a semisynthetic cephalosporin antibiotic for oral administration. It is chemically designated as 3-chloro-7-D-(2-phenylglycinamido)-3-cephem-4-carboxylic acid monohydrate.

$C_{15}H_{14}ClN_3O_4S.H_2O$
MW 385.82

Each capsule contains cefaclor monohydrate equivalent to 250 mg (0.65 mmol) or 500 mg (1.30 mmol) cefaclor.

Inactive Ingredients: sodium starch glycolate and sodium stearyl fumarate.

CAPSULE SHELL AND PRINT CONSTITUENTS: D&C Yellow #10 Aluminum Lake, FD&C Blue #1 Aluminum Lake, FD&C Blue #2 Aluminum Lake, FD&C Red #40, gelatin, pharmaceutical glaze, propylene glycol, silicon dioxide, sodium lauryl sulfate, synthetic black iron oxide and titanium dioxide. The 250 mg capsule shell also contains black iron oxide and yellow iron oxide.

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 three fourths to 1 1/2 hour 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 µg/mL 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 1,900 µg/mL 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 inhibition of cell-wall synthesis. Cefaclor is active *in vitro* against most strains of clinical isolates of the following organisms:

Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains (when tested by *in vitro* methods) exhibit cross-

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Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains (when tested by *in vitro* methods), exhibit cross-resistance between cefaclor and methicillin.

Streptococcus pyogenes (group A β-hemolytic streptococci)

Streptococcus pneumoniae

Moraxella (Branhamella) catarrhalis

Haemophilus influenzae, including β-lactamase-producing ampicillin-resistant strains

Escherichia coli

Proteus mirabilis

Klebsiella sp.

Citrobacter diversus

Neisseria gonorrhoeae

Propionibacterium acnes and *Bacteroides* sp. (excluding *Bacteroides fragilis*)

Peptococci

Peptostreptococci

Note: *Pseudomonas* sp., *Acinetobacter calcoaceticus* (formerly *Mima* sp. and *Herellea* sp.), and most strains of enterococci (*Enterococcus faecalis* [formerly *Streptococcus faecalis*], group D streptococci), *Enterobacter* sp., indole-positive *Proteus*, and *Serratia* sp. are resistant to cefaclor. When tested by *in vitro* methods, staphylococci exhibit cross-resistance between cefaclor and methicillin-type antibiotics.

Disk Susceptibility Tests—Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure* has been recommended for use with disks for testing susceptibility to cephalothin. The currently accepted zone diameter interpretative criteria for the cephalothin disk are appropriate for determining bacterial susceptibility to cefaclor. With this procedure, a report from the laboratory of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels can be obtained or if high dosage is used.

INDICATIONS AND USAGE

Cefaclor capsules are 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, and *S. pyogenes* (group A β-hemolytic streptococci)

Lower respiratory infections, including pneumonia, caused by *S. pneumoniae*, *H. influenzae*, and *S. pyogenes* (group A β-hemolytic streptococci)

Upper respiratory infections, including pharyngitis and tonsillitis, caused by *S. pyogenes* (group A β-hemolytic streptococci)

Note: Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 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 rheumatic fever are not available at present.

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

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

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

CONTRAINDICATIONS

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

WARNINGS

IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES.

Antibiotics, including cefaclor,

skin and skin structure infections caused by *Staphylococcus aureus* and *S. pyogenes* (group A β-hemolytic streptococci).

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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.

Treatment with broad-spectrum antibiotics 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.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out.

PRECAUTIONS

General—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.

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

Bauer AW, Kirby WMM, Sherris JC, and Turck M: Antibiotic susceptibility testing by a standardized single disk method. *Am J Clin Pathol* 1966;45:493. Standardized disk susceptibility test. *Federal Register* 1974;39:19182-19184.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. 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, it should be recognized that a positive Coombs' test may be due to the drug.

Cefaclor 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.

As with other β-lactam antibiotics, the renal excretion of cefaclor is inhibited by probenecid.

As a result of administration of cefaclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy—Pregnancy Category B—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 cefaclor. 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.

Nursing Mothers—Small amounts of cefaclor 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 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 cefaclor 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 cefaclor 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 39,000 (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

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.

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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, agitation, 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 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 warfarin concomitantly.

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

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—To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. 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 cefaclor 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

Renal—[illegible] serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200)

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

DOSAGE AND ADMINISTRATION

Cefaclor capsules are administered orally.

Adults—The usual adult dosage is 250 mg every 8 hours. For more severe infections (such as pneumonia) or those caused by less susceptible organisms, doses may be doubled.

Cefaclor 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 cefaclor should be administered for at least 10 days.

HOW SUPPLIED

Cefaclor Capsules, USP are supplied as follows:

250 mg: White opaque cap and gray opaque body, imprinted "BIOCRAFT 223", in bottles of 15 (NDC 0332-3206-24), 100 (NDC 0332-3206-09), 500 (NDC 0332-3206-13).

500 mg: Red opaque cap and white opaque body, imprinted "BIOCRAFT 224", in bottles of 15 (NDC 0332-3210-24), 100 (NDC 0332-3210-09), 500 (NDC 0332-3210-13).

Store at controlled room temperature 15° - 30°C (59° - 86°F).

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Manufactured by
Biocraft Laboratories, Inc.
Elmwood Park, NJ 07407

April 1994

NDC 0332-3210-24

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Lot # SEP 1 6 1996

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N 3 0332-3210-13 3

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LOT

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