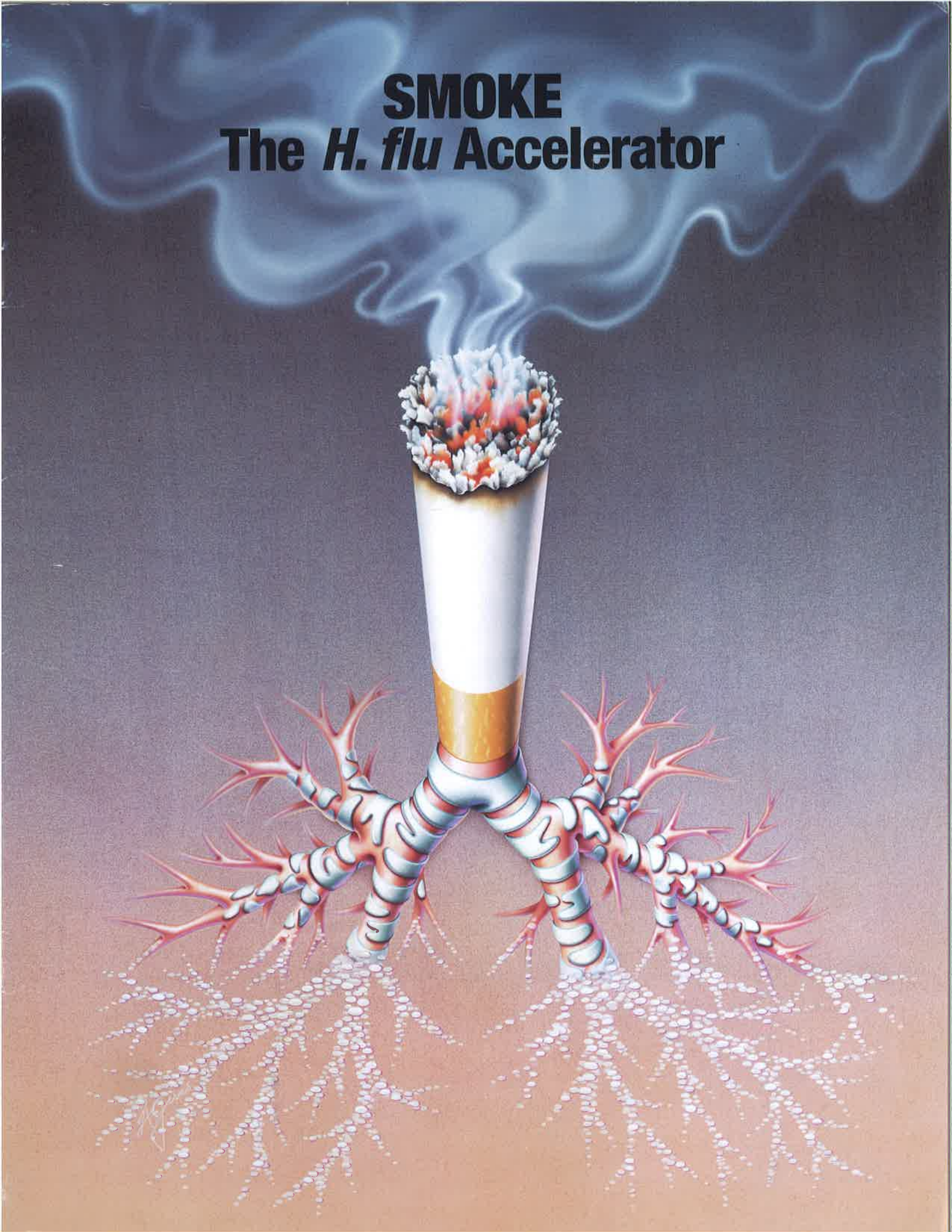
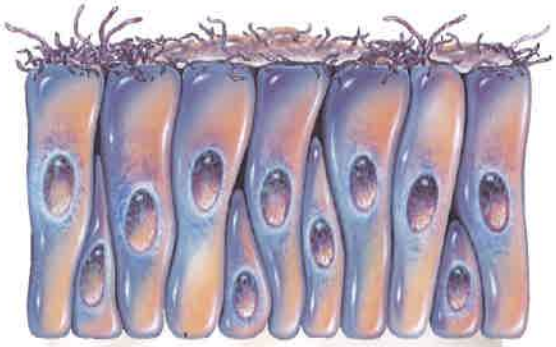
SMOKE
The *H. flu* Accelerator



As smoke accelerates the growth of *H. flu*...

- Smoke products, even in small quantities, stimulate growth of *Haemophilus influenzae*[1]
- *H. flu* binds to mucus and injures bronchial epithelium[2]
- *H. flu* toxins affect cilia by:
  - slowing them[3]
  - disorganizing them[3]
  - eventually stopping them[3]
- Mucociliary "escalator" becomes dysfunctional
  - mucus stagnates
  - *H. flu* is trapped and bound to epithelial surface
  - *H. flu* grows further, perpetuating the cycle[2]

...lung function decreases



- *H. flu* stimulates the production of histamine[4]
  - epithelium permeability increases, further increasing bacterial colonization
  - goblet cells step up mucus production, decrease lung clearance
  - bronchial smooth muscle constricts, exacerbating symptoms of chronic bronchitis

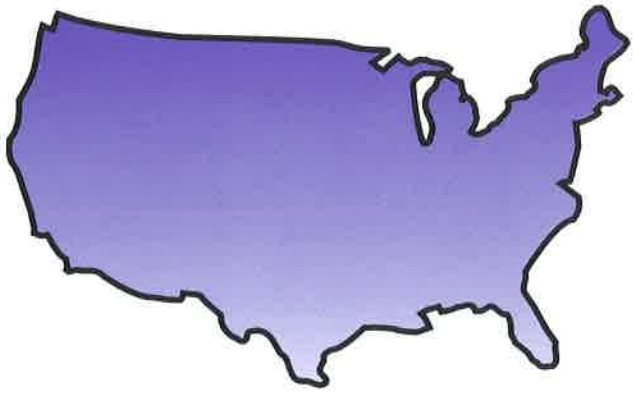
Where there's smoke, there may be risk of greater bronchial damage

"It is possible that the combination of an increase in the number of [*H. flu*] organisms due to stimulation of growth by nicotine (thereby producing more toxin) and impaired ability of the pulmonary macrophage to eliminate the organism may lead to increased bronchial mucosal damage in heavy smokers."[1]

Where there's smoke, there ought to be CECLOR®(cefaclor)

Demonstrated effectiveness against *H. flu* (ß-lactamase +/-)

- 98% overall susceptibility of more than 5000 *H. flu* isolates in 50 surveillance studies nationwide[5]



Confirmed potency against *H. flu* and the most common respiratory pathogens[6]

The following in vitro data are available, but their clinical significance is unknown.

Pathogen	Susceptibility to CECLOR* (%)
H. influenzae (ß-lactamase-negative)	**99** (469/471 isolates)
H. influenzae (ß-lactamase-positive)	**96** (89/93 isolates)
Streptococcus pneumoniae	**99.8** (486/487 isolates)
Moraxella catarrhalis (ß-lactamase-negative)	**100** (60/60 isolates)
M. catarrhalis (ß-lactamase-positive)	**100** (318/318 isolates)

*Includes intermediate susceptible strains.

Continued efficacy in chronic bronchitis, even in heavy smokers

"A decade of clinical experience with cefaclor [CECLOR]…demonstrates a continued high level of clinical and in vitro efficacy. [The present study confirms that]…cefaclor was highly effective in the treatment of infective exacerbations of chronic bronchitis, even in heavy smokers."[7]

Proven clinical success where it counts…in patients

95%	satisfactory clinical response* (174/184 patients, 250 mg TID) **in chronic bronchitis**[5†]
98%	satisfactory clinical response* (62/63 patients, 250 mg TID) **in bacterial bronchitis due to ß-lactamase-producing and -nonproducing *H. flu***[5]
96%	satisfactory clinical response* (51/53 patients, 250 mg TID) **in bacterial bronchitis due to *S. pneumoniae***[5]

*See gatefold for criteria for diagnosis and response.
†Due to susceptible strains of isolated organisms.

Where there's smoke, there ought to be

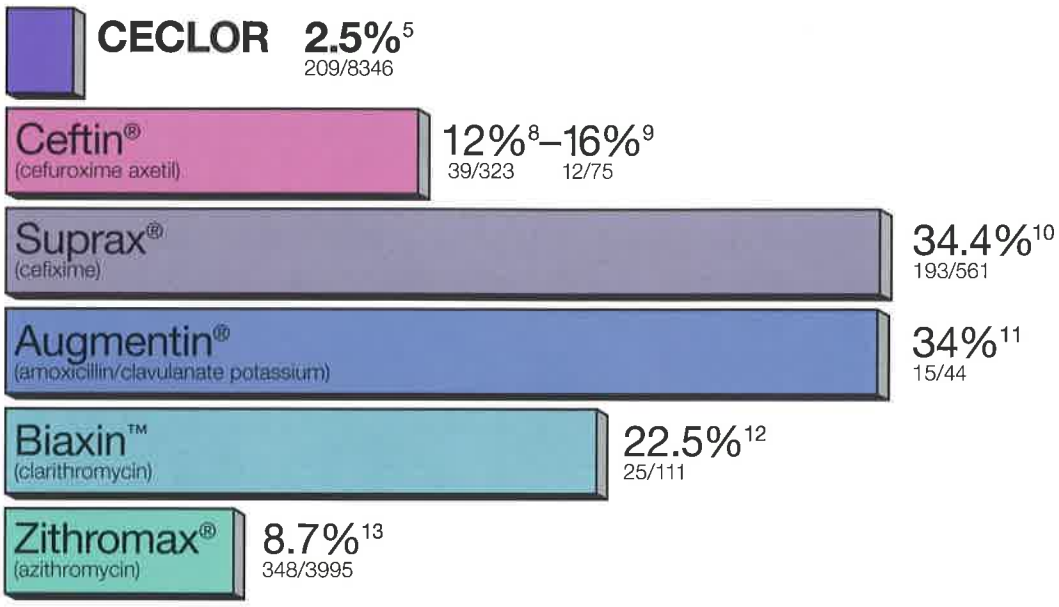
Ceclor®
cefaclor

The consistent drug for persistent bugs

CECLOR consistently well tolerated

Compare the GI side effects of selected antibiotics*

Incidence of GI side effects with CECLOR only 2.5%



*These data are not from directly comparative studies.

Low potential for drug-drug interactions[14]

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The facts about *Mycoplasma pneumoniae* in chronic bronchitis

The most common microorganisms in chronic bronchitis include[2]:

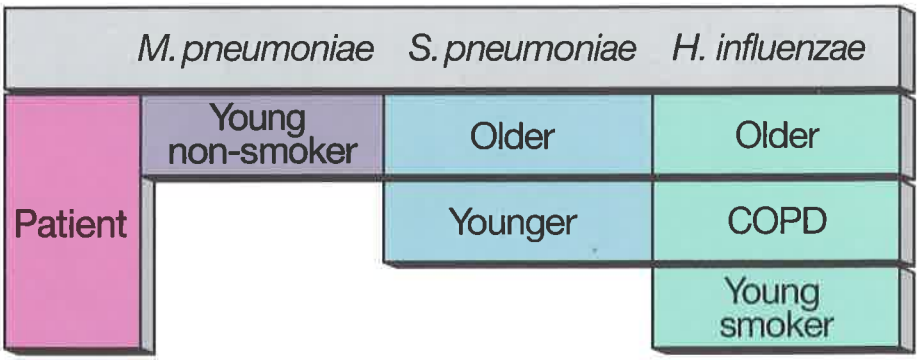
M. pneumoniae is usually not a concern in chronic bronchitis

Infections due to *M. pneumoniae* are usually:

- seen in younger patients[4]
- self-limiting[4]
- not seen in smokers[4,15]

Even young smokers are prone to the same type of infections as older patients or patients with COPD[4]

Major causative pathogens for LRTIs in outpatients[4]



Macrolides may be inadequate to treat the most common pathogens of chronic bronchitis

"In our [in vitro] experiments, *H. influenzae* would be categorized as being resistant to erythromycin, roxithromycin, and clarithromycin..."[16]

CECLOR: Potent against the major respiratory pathogens

The following in vitro data are available, but their clinical significance is unknown.

Susceptible to Ceclor[6]:

- **98%**: *H. influenzae* (ß-lactamase +/-)*
- **99.8%**: *S. pneumoniae*†
- **100%**: *M. catarrhalis* (ß-lactamase +/-)‡

*564 isolates †487 isolates ‡ 378 isolates

Where there's smoke, there ought to be

Ceclor®
cefaclor

The consistent drug for persistent bugs

References:

1. *J Clin Pathol.* 1979;32:728-731.
2. *Contemp Intern Med.* November 1993;5:8-16.
3. *Thorax.* 1985;40:125-131.
4. *JAOA.* 1992;92:897-905.
5. Data on file, Lilly Research Laboratories.
6. *Antimicrob Agents Chemother.* 1990;34:2075-2080.
7. *J Chemother.* 1991;3:245-249.
8. Royal Society of Medicine Services International Congress and Symposium Series No. 124. Royal Society of Medicine Services Limited;1987:45-52.
9. *Arch Otolaryngol Head Neck Surg.* 1989;115:1430-1433.
10. *Pediatr Infect Dis J.* 1987;6:976-980.
11. *Antimicrob Agents Chemother.* 1983;24:856-859.
12. *J Antimicrob Chemother.* 1991;27(suppl A):91-100.
13. *Clin Pharm.* 1992;11:137-152.
14. Manufacturer's prescribing information.
15. *Am Fam Physician.* 1987;36:133-140.
16. *Antimicrob Agents Chemother.* 1988;32:752-754.

Criteria for diagnosis and response

Lower respiratory infections caused by susceptible strains of isolated organisms, including *S. pneumoniae, H. influenzae* (ampicillin-susceptible and ampicillin-resistant), and S. pyogenes (group A β-hemolytic streptococci). For bronchitis patients, the culture source was sputum or transtracheal aspirate. Pretherapy x-rays were obtained for all patients.

Clinical (symptomatic) response

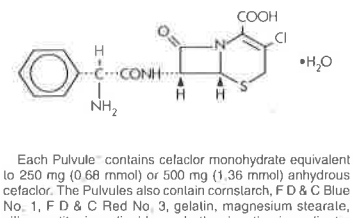
Satisfactory — Disappearance of or improvement in signs and symptoms of the principal infection, with or without recurrence of signs or symptoms during the posttherapy follow-up period.

Unsatisfactory — No improvement in signs and symptoms at the end of therapy.

Ceclor®

cefaclor

Description: Ceclor 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. The chemical formula for cefaclor is $C_{15}H_{14}ClN_3O_4S{\cdot}H_2O$ and the molecular weight is 385.82.



Each Pulvule® contains cefaclor monohydrate equivalent to 250 mg (0.68 mmol) or 500 mg (1.36 mmol) anhydrous cefaclor. The Pulvules also contain cornstarch, F D & C Blue No. 1, F D & C Red No. 3, gelatin, magnesium stearate, silicone, titanium dioxide, and other inactive ingredients. The 500-mg Pulvule also contains iron oxide.

After mixing, each 5 mL of Ceclor for Oral Suspension will contain cefaclor monohydrate equivalent to 125 mg (0.34 mmol), 187 mg (0.51 mmol), 250 mg (0.68 mmol), or 375 mg(1.0 mmol) anhydrous cefaclor. The suspensions also contain cellulose, cornstarch, F D & C Red No. 40, flavors, silicone, sodium lauryl sulfate, sucrose, and xanthan gum.

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 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-resistance between cefaclor and methicillin
- *Streptococcus pyogenes* (group A β-hemolytic streptococci)
- *Streptococcus pneumoniae*
- *Moraxella catarrhalis* (formerly *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* sp., 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[1] 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 (eg, urine) in which high antibiotic levels can be obtained or if high dosage is used.

Indications and Usage: 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, 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. Ceclor is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of Ceclor 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 Ceclor.

Contraindication: Ceclor 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 Ceclor, 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 Ceclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, eg, pressor amines, antihistamines, or corticosteroids.

Prolonged use of Ceclor 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.

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.

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.

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

As a result of administration of Ceclor, 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, Lilly).

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

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 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.

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 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 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 Ceclor. 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 Ceclor. Such reactions have been reported more frequently in children than in adults with an overall occurrence ranging from 1 in 200 (0.5%) in 1 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, 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 Ceclor and Coumadin 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 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 more severe infections (such as pneumonia) or those caused by less susceptible organisms, doses may be doubled.

Children—The usual recommended daily dosage for children is 20 mg/kg/day in divided doses every 8 hours. In more serious infections, otitis media, and infections caused by less susceptible organisms, 40 mg/kg/day is recommended, with a maximum dosage of 1 g/day.

Ceclor Suspension

Child's Weight	20 mg/kg/day 125 mg/5 mL	250 mg/5 mL
9 kg	1/2 tsp t.i.d.	
18 kg	1 tsp t.i.d.	1/2 tsp t.i.d.
	40 mg/kg/day	
9 kg	1 tsp t.i.d.	1/2 tsp t.i.d.
18 kg		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.

Ceclor Suspension

Child's Weight	20 mg/kg/day (Pharyngitis) 187 mg/5 mL	375 mg/5 mL
9 kg	1/2 tsp b.i.d.	
18 kg	1 tsp b.i.d.	1/2 tsp b.i.d.
	40 mg/kg/day (Otitis Media)	
Child's Weight	187 mg/5 mL	375 mg/5 mL
9 kg	1 tsp b.i.d.	1/2 tsp b.i.d.
18 kg		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.

How Supplied:

Pulvules:

250 mg, purple and white (No. 3061)—(RxPak* of 15) NDC 0002-3061-15; (100s) NDC 0002-3061-02; (ID† 100) NDC 0002-3061-33

500 mg, purple and gray (No. 3062)—(RxPak of 15) NDC 0002-3062-15; (100s) NDC 0002-3062-02; (ID 100) NDC 0002-3062-33

For Oral Suspension:

125 mg/5 mL, strawberry flavor (M-5057‡)—(75-mL size) NDC 0002-5057-18; (150-mL size) NDC 0002-5057-68

187 mg/5 mL, strawberry flavor (M-5130‡)—(50-mL size) NDC 0002-5130-87; (100-mL size) NDC 0002-5130-48

250 mg/5 mL, strawberry flavor (M-5058‡)—(75-mL size) NDC 0002-5058-18; (150-mL size) NDC 0002-5058-68

375 mg/5 mL, strawberry flavor (M-5132‡)—(50-mL size) NDC 0002-5132-87; (100-mL size) NDC 0002-5132-48

* All RxPaks (prescription package, Lilly) have safety closures.
† Identi-Dose® (unit dose medication, Lilly)
‡ After mixing, store in a refrigerator. Shake well before using. Keep tightly closed. The mixture may be kept for 14 days without significant loss of potency. Discard unused portion after 14 days.
Store at controlled room temperature, 59° to 86°F (15° to 30°C).

1. *Am J Clin Pathol* 1966;45:493; *Federal Register* 1974; 39:19182-19184.

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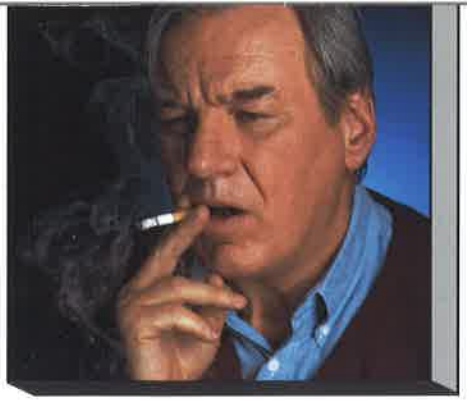

Because in the lung, smoke is the *H. flu* accelerator... CECLOR

- **Potent:**
  Demonstrated highly effective against the most common lower respiratory pathogens
- **Effective:**
  Highly effective in the treatment of infective exacerbations of chronic bronchitis, even in heavy smokers
- **Gentle:**
  Consistently low incidence of GI side effects
- **Predictable:**
  Low potential for drug-drug interactions

Where there's smoke, there ought to be

Ceclor®
cefaclor

The consistent drug for persistent bugs

Eli Lilly and Company
Indianapolis, Indiana
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