

AUSTRALIAN PRODUCT INFORMATION

CECLOR CD (CEFACLOR MONOHYDRATE)

SUSTAINED RELEASE TABLET

1 NAME OF THE MEDICINE

Cefaclor monohydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sustained release tablet contains cefaclor monohydrate equivalent to 375 mg (1.02mmol) anhydrous cefaclor. The tablets also contain the inactive ingredients mannitol, hypromellose, hypromellose, methacrylic acid copolymer, stearic acid, magnesium stearate, propylene glycol, purified talc and Color Mixture Dark Blue YS-1-4273.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Sustained release tablet

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CECLOR CD is indicated for the treatment of the following types of infections caused by susceptible organisms, in adults and children aged 12 years or older.

Acute bronchitis and acute exacerbations of chronic bronchitis.

Upper respiratory infections, including pharyngitis, tonsillitis and acute bacterial sinusitis.

Community-acquired pneumonia of mild to moderate severity (excluding atypical pneumonia).

Symptomatic lower urinary tract infections, including cystitis.

Skin and skin structure infections.

NOTE:

1. Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. CECLOR CD is generally effective in the eradication of streptococci from the oropharynx; however, substantial data establishing

the efficacy of CECLOR CD in the subsequent prevention of rheumatic fever are not available.

2. 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

CECLOR CD can be taken with or without food. However, absorption is enhanced when CECLOR CD is administered with food (see Section 5.2 Pharmacokinetic Properties). The tablets should not be cut, crushed or chewed.

The usual adult dosage is 375 mg twice daily.

For lower urinary tract infections, 500 mg once daily may be given. For pneumonia and acute bacterial sinusitis, the recommended dosage is 750 mg twice daily. For acute bacterial sinusitis, CECLOR CD should be taken for 10 days.

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

For patients with markedly impaired renal function (see Section 4.4 Special Warnings and Precautions for Use).

4.3 CONTRAINDICATIONS

CECLOR CD is contraindicated in patients with known allergy to the cephalosporin group of antibiotics or who have previously experienced a major allergy to penicillin (see Section 4.4 Special Warnings and Precautions for Use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

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. Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid) reactions have been reported in patients on penicillin/cephalosporin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins/cephalosporins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a

history of penicillin/cephalosporin hypersensitivity who have experienced severe reactions when treated with a penicillin/cephalosporin.

Past history of a severe allergic reaction to penicillin/cephalosporin is a contraindication to the use of CECLOR CD. Before initiating therapy with any cephalosporin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, CECLOR CD should be discontinued and the appropriate therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management, including intubation, should also be administered as indicated.

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

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including cefaclor. A toxin produced with *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *C. difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, eg. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

As with antibiotic therapy in general, administration of CECLOR CD should be continued for a minimum of 48 to 72 hours after the patient becomes asymptomatic or after evidence of bacterial eradication has been obtained. A minimum of ten days of treatment is recommended in infections caused by group A beta-haemolytic streptococci in order to guard against the risk of rheumatic fever or glomerulonephritis.

Prolonged use of CECLOR CD 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.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients

taking beta-lactam antibiotics. When SCAR is suspected, Ceclor CD should be discontinued immediately and an alternative treatment should be considered.

Use in hepatic impairment

CECLOR CD should be used with caution in patients with liver disease, as documented clinical experience in this group of patients is lacking.

Use in renal impairment

CECLOR CD 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.

Use in the elderly

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 are not expected to have clinical significance. Therefore, dosage changes are not necessary in elderly subjects with normal renal function.

Paediatric use

The safety and efficacy of CECLOR CD has not been studied in children. **Serum sickness-like reactions including arthritis and arthralgia have been reported more frequently in children than in adults with the use of cefaclor.**

Effects on laboratory tests

Administration of CECLOR CD 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).

Positive direct Coombs' tests have been reported during treatment with CECLOR. In haematologic studies or in transfusion cross-matching procedures when anti-globulin tests are performed on the minor side, or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognised that a positive Coombs' test may be due to the drug.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The extent of absorption of CECLOR CD is diminished if magnesium- or aluminium hydroxide-containing antacids are taken within 1 hour of administration; cimetidine did not alter either the rate or the extent of absorption of CECLOR CD. As with other β -lactam antibiotics, the renal excretion of CECLOR (and presumably CECLOR CD) is inhibited by probenecid. No other significant drug interactions were noted during clinical trials.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Reproduction studies have revealed no evidence of impaired fertility.

Use in pregnancy – Pregnancy Category B1

The oral administration of high dose cefaclor (500 mg/kg) in pregnant rats and mice has resulted in a slight increase of minor skeletal malformations. Safety of this product for use during pregnancy has not been established. Cefaclor should not be used in women of child bearing potential unless, in the judgement of the treating clinician, its use is considered essential to the welfare of the patient and the expected benefits outweigh potential risks.

Labour and Delivery -- CECLOR CD has not been studied for use during labour and delivery. Treatment should be given only if clearly needed.

Use in lactation

No studies have been done with CECLOR CD. Small amounts of cefaclor have been detected in mother's milk following administration of single 500 mg doses of CECLOR. Average levels were 0.18, 0.20, 0.21 and 0.16 $\mu\text{g}/\text{mL}$ 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 CD is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

The majority of adverse reactions observed in clinical trials of CECLOR CD 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 CD in clinical trials. Incidence rates were less than 1%, except as otherwise noted.

Gastrointestinal: Diarrhoea (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 CD during the controlled clinical trials.

Haematologic and Lymphatic Systems: Eosinophilia.

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

Acute bacterial sinusitis:

Adverse experiences reported among patients with acute bacterial sinusitis treated with CECLOR CD (750 mg bid) or CECLOR capsules (500 mg tid) during a controlled clinical trial are shown in the table below. Included are all adverse experiences occurring with an incidence of 2% or greater in either treatment group.

EVENT CLASSIFICATION TERM	CECLOR CD N=147	CECLOR N=150
HEADACHE	8 (5.4%)	4 (2.7%)
DIARRHOEA	6 (4.1%)	4 (2.7%)
ABDOMINAL PAIN	5 (3.4%)	7 (4.7%)
ASTHENIA	3 (2.0%)	5 (3.3%)
EPISTAXIS	3 (2.0%)	0 (0.0%)
PAIN	3 (2.0%)	1 (0.7%)
VAGINITIS	2 (1.4%)	3 (2.0%)

The following adverse effects have been reported in patients treated with CECLOR CD; causal relationship is uncertain. Incidence rates were less than 1%, except as otherwise noted.

Central Nervous System: Headache (3.2%), dizziness and somnolence.

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

Renal: Transient increase in serum urea or creatinine.

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

In addition, the following adverse reactions and altered laboratory tests have been reported in patients treated with CECLOR:

Cases of serum-sickness-like reactions have been reported with the use of cefaclor. These have been reported more frequently in children than in adults with an overall occurrence ranging from 0.5% (1 in 200) in one trial, to 0.024% (2 in 8,346) in overall clinical trials (with an incidence in children in clinical trials of 0.055%). The worldwide reporting rate for serum-sickness-like reactions in adults is very rare (<0.01%). **Serum-sickness-like reactions are characterised 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. 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 hospitalisation usually of short duration (median hospitalisation = 2 to 3 days, based on postmarketing surveillance studies). In those requiring hospitalisation, 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 and toxic epidermal necrolysis have been reported rarely. Anaphylaxis may be more common in patients with a history of penicillin allergy. The worldwide reporting rate for anaphylaxis in the total population is very rare (<0.01%). Positive direct Coombs' test and genital pruritus

have been reported. Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.

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

Reversible interstitial nephritis, hepatic dysfunction including hepatitis and cholestatic jaundice, increased prothrombin time in patients receiving CECLOR and warfarin concomitantly, reversible hyperactivity, nervousness, insomnia, confusion, hallucinations, hypertonia, haemolytic anaemia, agranulocytosis, aplastic anaemia, fever and angioedema.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected, Ceclor CD should be discontinued immediately and an alternative treatment should be considered.

4.9 OVERDOSE

Signs and Symptoms -- The toxic symptoms following an overdose of CECLOR CD may include nausea, vomiting, epigastric distress and diarrhoea. The severity of the epigastric distress and the diarrhoea 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. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing charcoal.

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Microbiology

The in vitro bactericidal activity of CECLOR CD 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 β -lactamases; consequently, β -lactamase-producing organisms resistant to penicillins and some cephalosporins may be susceptible to cefaclor. Cefaclor has been shown to be active against most strains of the following organisms both in vitro and in clinical infections:

Gram-positive organisms:

Staphylococcus aureus

Staphylococcus saprophyticus

Streptococcus pneumoniae

Streptococcus pyogenes (group A streptococci)

NOTE: Cefaclor is inactive against methicillin-resistant staphylococci.

Gram-negative organisms:

Haemophilus influenzae

Moraxella (Branhamella) catarrhalis

Escherichia coli

Klebsiella pneumoniae

Proteus mirabilis

NOTE: *Pseudomonas sp*, *Acinetobacter calcoaceticus*, enterococci, *Enterobacter sp*, indole-positive *Proteus* and *Serratia sp* are resistant to cefaclor.

Susceptibility Testing --

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Clinical trials

No data is available

5.2 PHARMACOKINETIC PROPERTIES

CECLOR CD is well absorbed from the gastrointestinal tract after oral administration. Although CECLOR CD can be taken with or without food, total absorption is enhanced with food. When it was given within one hour after a meal, the bioavailability of CECLOR CD was greater than 90%, using CECLOR taken fasting as a reference. When taken in the fasting state, the bioavailability of CECLOR CD was 77% that of CECLOR. Compared to CECLOR (fasted state), mean peak plasma concentrations of CECLOR CD (both fed and fasted states) were delayed 40 to 90 minutes and were lower. Concomitant administration of cimetidine does not affect the rate or extent of absorption. Administration of magnesium- or aluminium hydroxide-containing antacids 1 hour after CECLOR CD had no effect on the rate of absorption but resulted in a 17% decrease in the extent of absorption. The effect of antacids taken at other times is uncertain.

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 for 2½ days.

The plasma half-life in healthy subjects is independent of dosage form and averages 40-60 minutes. 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 are not expected to have 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data is available

Carcinogenicity

Studies in animals have not been performed to evaluate the carcinogenic or mutagenic potential for CECLOR CD.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25 degrees Celsius and protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

375 mg tablets (sustained release): Blue capsule shaped tablets with no engraving in PVC/PCTFE (Aclar)/Al blister packs.

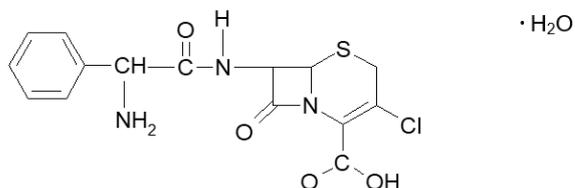
Packs of 2 (sample packs) or 10.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CECLOR CD (cefaclor sustained release) is a pharmaceutically-modified form of the orally active cephalosporin, cefaclor monohydrate. It is a semisynthetic cephalosporin antibiotic for oral administration. The active ingredient is chemically designated as 3-chloro-7-D-(2-phenyl- glycinamido)-3-cephem-4-carboxylic acid monohydrate. CECLOR CD differs from other available products containing 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.

CAS number: 70356-03-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

Aspen Pharmacare Australia Pty Ltd

34-36 Chandos St

St Leonards NSW 2065

9 DATE OF FIRST APPROVAL

7 AUGUST 1996

10 DATE OF REVISION

16 July 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Product Information reformatted to TGA's updated guidelines
4.4, 4.8	Addition of "severe cutaneous adverse reactions"; "skin and other subcutaneous tissue disorders"