Product Information – Australia

GenRx CEFACLOR SUSPENSION

NAME OF THE MEDICINE
Cefaclor monohydrate

Chemical name:  3-chloro-7-D-(2-phenylglycinamido)-3-cephem-4-carboxylic acid monohydrate.

Structural formula:

![Structural formula](attachment:image)

Molecular formula:  C_{15}H_{14}ClN_{3}O_{4}S.H_{2}O.
Molecular Weight:  385.8
CAS Registry number:  70356-03-5.

DESCRIPTION
Cefaclor monohydrate is a white to off-white crystalline powder, slightly soluble in water, but is insoluble in alcohol and chloroform.

PHARMACOLOGY
Cefaclor is a semisynthetic, broad spectrum cephalosporin antibiotic for oral administration.

Pharmacokinetics
Cefaclor is well absorbed after oral administration, whether taken with food or while fasting. 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. The presence of food in the gastrointestinal tract does not alter the total amount of cefaclor absorbed. Following administration of 250 mg, 500 mg and 1 g doses to fasting subjects, average peak plasma levels of antibacterial activity (expressed as µg/mL of cefaclor) of 7, 13 and 23 µg/mL, respectively, were obtained at 30 to 60 minutes. The reduced peak serum levels resulting from the administration of cefaclor with food should be considered with reference to the sensitivity of the infecting organism, severity of illness, the dose being administered and the variability in the peak plasma levels which occur with cefaclor.

The plasma half-life in healthy subjects is independent of dosage form and averages 40 to 60 minutes. In elderly subjects (>65 years) with normal serum creatinine values, a higher peak plasma concentration and area under the curve are effects resulting from mildly diminished renal function and are not expected to have clinical significance. Therefore dosage change is not necessary in elderly subjects with normal renal function. There is no evidence of metabolism of cefaclor in humans.
Microbiology

*In vitro* tests demonstrate that the bactericidal action of the 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 may have useful activity against the following organisms *in vitro* and in clinical infections:

- Staphylococci, including coagulase positive and penicillinase producing strains (but not methicillin resistant strains of *Staphylococcus aureus*);
- *Streptococcus pyogenes* (group A β-haemolytic Streptococci), *Streptococcus (Diplococcus) pneumoniae*;
- *Escherichia coli*;
- *Proteus mirabilis*;
- *Klebsiella* sp;
- *Haemophilus influenzae*;
- *Neisseria gonorrhoeae* (penicillinase and non-penicillinase producing strains);
- *Moraxella (Branhamella) catarrhalis*.

Note: Pseudomonas sp., *Acinetobacter calcoaceticus*, Enterococci, Enterobacter sp., indole-positive Proteus, and Serratia sp. are resistant to cefaclor. Methicillin resistant strains are also 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.
INDICATIONS

Infections due to susceptible microorganisms:

- **Lower respiratory infections**, including pneumonia, bronchitis and exacerbations of chronic bronchitis
- **Upper respiratory tract infections**, including pharyngitis, tonsillitis and otitis media
- **Skin and skin structure infections.**
- **Urinary tract infections**, including pyelonephritis and cystitis.

Note:

1. Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Cefaclor appears to be as effective as phenoxymethylpenicillin 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.

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

CONTRAINDICATIONS

- Known allergy to cephalosporins or previous experience of a major allergy to penicillin (see PRECAUTIONS) or any of the excipients listed (see PRESENTATION AND STORAGE CONDITIONS).

- Infants under the age of 1 month; safety and efficacy of this product have not been established in premature infants and infants under 1 month of age.

PRECAUTIONS

*Except under special circumstances, this medication should not be used when the following medical problem exists:*

**Penicillin Sensitive Patients, or those with Hypersensitivity to Other Allergens.**

Cephalosporin antibiotics should be administered cautiously in this patient group. 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.

**Severe Allergic Reaction to Penicillin or Cephalosporin Class of Drugs, or other Allergens**

Past history of a severe allergic reaction to drug from the penicillin or cephalosporin group of drugs is a contraindication to the use of cefaclor. 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, cefaclor 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.

**History of Colitis or Gastrointestinal Disease**

Broad spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, especially ulcerative colitis, regional enteritis, or antibiotic-associated colitis.
Risk-benefit should be considered when the following medical problems exist:

Pseudomembranous 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 Clostridium difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil), may prolong and/or worsen the condition and should not be used.

History of bleeding disorders
All cephalosporins may cause hypoprothrombinaemia and, potentially, bleeding.

Adequate Treatment Period
As with antibiotic therapy in general, administration of cefaclor 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 10 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 Cefaclor
This 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.

Impaired Renal Function
Many cephalosporins are excreted renally. 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.

Impaired Hepatic Function
Cefaclor should be used with caution in patients with hepatic disease, as documented clinical experience in this group of patients is lacking.

Effects on Fertility
Adequate and well-controlled studies in humans have not been done. Reproduction studies have revealed no evidence of impaired fertility.

Use in 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 malformation. Cefaclor should not be used in women of childbearing potential unless, in the judgment of the treating physician, its use is considered essential to the welfare of the patient and the expected benefits outweigh potential risks.

Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

Labour and Delivery
Cefaclor has not been studied for use during labour and delivery. Treatment should be given only if clearly needed.
Use in Lactation
Small amounts of cefaclor have been detected in breast 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 breastfed infants is not known. Caution should be exercised when cefaclor is administered to a breastfeeding woman.

Use in Children
Safety and effectiveness of this product for use in infants less than 1 month of age have not been established. Serum sickness-like reactions including arthritis and arthralgia have been reported more frequently in children than in adults.

Use in the Elderly
Cephalosporins have been used in the geriatric population, and no geriatrics-specific problems have been documented to date. However, elderly patients are more likely to have an age-related decrease in renal function, which may require and adjustment in dosage and/or dosing interval in patients receiving cephalosporins.

Dental
Long-term therapy with cephalosporins may allow for the overgrowth of Candida albicans, resulting in oral candidiasis.

Interactions with Other Medicines
Anti-coagulants, Coumarin- or Indandione-derivative, or Heparin or Thrombolytic Agents
Because all cephalosporins can inhibit vitamin K synthesis by suppressing gut flora, prophylactic vitamin K therapy is recommended when any of these medications is used for prolonged periods in malnourished or seriously ill patients.

Platelet Aggregation Inhibitors
Hypoprothrombinaemia induced by large doses of salicylates and/or cephalosporins, and the gastrointestinal ulcerative or hemorrhagic potential of non-steroidal anti-inflammatory drugs (NSAIDs), salicylates, or sulfinpyrazone may increase the risk of haemorrhage.

Antacids: The extent of absorption of cefaclor is diminished if magnesium or aluminium hydroxide containing antacids are taken within one hour of administration.

Probenecid
Probenecid decreases renal tubular secretion of those cephalosporins excreted by this mechanism, resulting in increased and prolonged cephalosporin serum concentrations, prolonged elimination half-life, and increased risk of toxicity.

Effect on Laboratory Tests
Glucose, Urine
Administration of cefaclor 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).

Coombs’ (antiglobulin) tests:
Positive direct Coombs’ tests have been reported during treatment with cefaclor. In haematological studies or in transfusion cross matching procedures when antiglobulin tests are performed on the minor side or in Coombs’ testing of newborn infants whose mothers have received cephalosporin antibiotics before parturition, it should be recognised that a positive Coombs’ test may be due to the drug.

Prothrombin time (PT):
May be prolonged.

Creatinine (serum):
Concentrations may be increased.
Carnitine or Haematocrit:
Values may decrease during therapy.

ADVERSE EFFECTS

Gastrointestinal
The most frequent side effect has been diarrhoea. Nausea and vomiting have been reported rarely. Colitis, including rare instances of pseudomembranous colitis, has been reported in conjunction with therapy with cefaclor (see PRECAUTIONS). Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.

Immune system disorders
Allergic reactions, such as urticaria and morbilliform eruptions, have been observed, as have pruritus and positive Coombs’ tests. These reactions usually subsided upon discontinuation of the drug. Angioedema and fever have been reported rarely.

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, toxic epidermal necrolysis and anaphylaxis, 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 (<0.001%).

Anaphylactoid events may present as solitary symptoms, including angioedema, asthenia, oedema (including face and limbs), dyspnoea, paraesthesias, syncope, or vasodilatation.

Rarely, hypersensitivity symptoms may persist for several months.

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

Hepatobiliary disorders.
Hepatic dysfunction, including transient hepatitis and cholestatic jaundice have been reported rarely.
Blood and Lymphatic System Disorders
Eosinophilia, transient lymphocytosis leucopenia and, rarely, thrombocytopenia, thrombocytosis, haemolytic anaemia, aplastic anaemia, 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 warfarin concomitantly.

There have also been reports of transient fluctuations in leucocyte count, predominantly lymphocytosis in infants and young children.

Renal and Urinary Disorders
Slight elevation in serum urea or serum creatinine or abnormalities of urinalysis (haematuria; pyuria), reversible interstitial nephritis.

Superinfection
Genital pruritus, moniliasis or vaginitis.

Nervous System Disorders
Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, hallucinations, headache or somnolence have been reported.

Other
Transitory abnormalities in clinical laboratory test results have been reported, but their clinical significance is uncertain. These include slight elevations in AST, ALT or alkaline phosphatase values; and slight elevations in serum urea or serum creatinine or abnormalities of urinalysis (haematuria, pyuria).

The following adverse reactions have been reported in patients treated with other beta-lactam antibiotics:
Renal dysfunction, and toxic nephropathy.
Several beta-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.

DOSAGE AND ADMINISTRATION
Administer orally.

Reconstitution of Oral Suspension
For 125mg/5mL bottles add 70 mL water, in two portions, to the granular powder. Shake well after each addition.
For 250mg/5mL bottles add 53 mL water, in two portions, to the granular powder. Shake well after each addition.

The reconstituted suspension should be stored under refrigeration at 2-8°C. The suspension may be kept for 14 days without significant loss of potency.

Adults
The usual adult dosage is 250 mg every eight to twelve hours. For bronchitis and pneumonia, the dosage is 250 mg three times daily. For more severe infections or those caused by less susceptible organisms, doses may be doubled (500 mg every eight hours).

Doses of 2 g daily should not be exceeded.
For skin and skin structure infections, the dosage is 250 mg two to three times daily.

Children
The usual recommended daily dosage for children with mild to moderate infections is 20 mg/kg/day in divided doses every 8 hours. The maximum dose is 1 g daily.
For streptococcal pharyngitis or tonsillitis and impetigo, administration every twelve hours appears equally effective.

In more serious infections, otitis media and infections caused by less susceptible organisms, the recommended dosage is 40 mg/kg/day in divided doses every eight to twelve hours (maximum 2 g/day). For otitis media, administration every twelve hours appears equally effective.

**Renal Impairment**

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

**β-haemolytic Streptococcal Infections**

In the treatment of β-haemolytic streptococcal infections, a therapeutic dosage of cefaclor should be administered for at least ten days.

**OVERDOSAGE**

**Symptoms**
The toxic symptoms following an overdose of cefaclor 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 the 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, haemodialysis or charcoal haemoperfusion have not been established as beneficial for an overdose of cefaclor.

Contact the Poison Information Centre on 13 11 26 (Australia) for advice on the management of overdosage.

**PRESENTATION AND STORAGE CONDITIONS**

**GenRx Cefaclor Oral Suspension 125mg/5mL:** White to off-white granular powder which forms a red strawberry flavoured suspension upon reconstitution with 70 mL water.

Bottles of 100 mL when reconstituted
AUST R Number: 169116

**GenRx Cefaclor Oral Suspension 250mg/5mL:** white to off-white granular powder which forms a red strawberry flavoured suspension upon reconstitution with 53 mL water.

Bottles of 75 mL when reconstituted
AUST R Number: 169117

**GenRx Cefaclor Oral Suspension** contains either 125 mg or 250 mg cefaclor per 5mL when reconstituted.
It is intended for oral administration.

In addition it contains the following inactive ingredients: xanthan gum (E415), sodium benzoate (E211), sucrose, colloidal anhydrous silica, allura red AC, proprietary strawberry flavouring (ARTG 2982), sodium citrate (E331), anhydrous citric acid (E330) and simethicone emulsion.

**Powder:** Store below 25°C. Protect from light and moisture.

**After Mixing:** Store in a refrigerator (2-8°C. Refrigerate. Do not freeze). Discard unused suspension after 14 days.

**NAME AND ADDRESS OF THE SPONSOR**

Apotex Pty Ltd
16 Giffnock Avenue
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**POISON SCHEDULE OF THE MEDICINE**

S4: Prescription Only Medicine.

**Date of TGA approval:** 26 February 2010

**Date of most recent amendment:** 30 June 2012