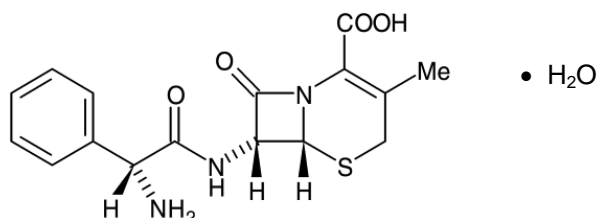


**APO-CEPHALEXIN POWDER FOR SUSPENSION****NAME OF THE MEDICINE**

Active Ingredients: Cephalexin monohydrate

Chemical Name: (6R,7R)-7-[(R)-2-amino-2-phenylacetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate

Structural Formula:



Molecular Formula:  $C_{16}H_{17}N_3O_4S \cdot H_2O$

Molecular Weight: 365.41

CAS Registry Number: 23325-78-2

**DESCRIPTION**

A semi-synthetic cephalosporin antibiotic for oral administration. The nucleus of cephalexin is related to that of other cephalosporin antibiotics. The compound is a zwitterion; i.e. the molecule contains both a basic and an acidic group. The isoelectric point of cephalexin in water is approximately 4.5 to 5. The crystalline form of cephalexin, which is available, is a monohydrate. It is a white or almost white crystalline solid having a bitter taste. Solubility in water is about 1% at room temperature. It is practically insoluble in alcohol and in ether. The cephalosporins differ from penicillins in the structure of the bicyclic ring system. Cephalexin has a D-phenylglycyl group as substituent at the 7-amino position and an unsubstituted methyl group at the 3-position.

**PHARMACOLOGY****Pharmacokinetics**

Cephalexin is acid stable and may be given without regard to meals. It is rapidly absorbed after oral administration. Following a dose of 500 mg, average peak serum levels of approximately 19 µg/mL were obtained at one hour. Measurable levels were present six hours after administration. Cephalexin is excreted in the urine by glomerular filtration and tubular secretion. Studies have shown that over 90% of the drug is excreted unchanged in the urine within 8 hours. During this period, reported peak urine concentrations following 250 mg, 500 mg and 1 g doses were approximately 1,000, 2,200 and 5,000 µg/mL, respectively.

**Microbiology**

*In vitro* tests demonstrate that the cephalosporins are bactericidal because they inhibit cell wall synthesis. Cephalexin is active against the following organisms *in vitro*: β-haemolytic Streptococci, Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase producing strains, *Streptococcus (Diplococcus) pneumoniae*, *Escherichia coli*, *Proteus mirabilis*, *Klebsiella* sp.

Note: Most strains of Enterococci (*Enterococcus faecalis*) and a few strains of Staphylococci are resistant to cephalexin. It is not active against most strains of *Enterobacter* sp., *Morganella morganii* (formerly *Pr. morganii*), and *Pr. vulgaris*.

It has no activity against *Pseudomonas* or *Acinetobacter calcoaceticus* (formerly *Mima* and *Herellea* sp.). When tested by *in vitro* methods, Staphylococci exhibit cross resistance between cephalexin and methicillin type antibiotics.

#### Disc Susceptibility Tests

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**

Treatment of the following infections when caused by susceptible strains of the designated microorganisms.

### **Respiratory Tract Infections**

Caused by *S. pneumoniae* and group A  $\beta$ -haemolytic Streptococci (penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Cephalexin is generally effective in the eradication of Streptococci from the nasopharynx; however, substantial data establishing the efficacy of cephalexin in the subsequent prevention of rheumatic fever are not available at present).

### **Bacterial Sinusitis**

Caused by Streptococci, *S. pneumoniae* and *S. aureus* (methicillin sensitive only).

### **Otitis Media**

Due to *S. pneumoniae*, Staphylococci.

### **Skin and Skin Structure Infections**

Caused by Staphylococci and/or Streptococci.

### **Genitourinary Tract Infections, Including Acute Prostatitis**

Caused by *E. coli*, *P. mirabilis* and *Klebsiella* sp.

The effectiveness of cephalexin in the treatment of bacterial infections of the brain and spinal column has not been established and cephalexin is not indicated in these conditions.

Note: Appropriate culture and susceptibility tests should be initiated prior to and during therapy to determine susceptibility of the causative organism to cephalexin. Renal function studies should be performed when indicated.

## **CONTRAINDICATIONS**

Known allergy to the cephalosporin group of antibiotics or previous experience of a major allergy to penicillin (see **PRECAUTIONS**).

## PRECAUTIONS

Before instituting therapy with cephalexin, every attempt should be made to determine if the patient has had previous hypersensitivity reactions to the cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin sensitive patients.

There is some clinical and laboratory evidence of partial cross allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

If an allergic reaction to cephalexin occurs, the drug should be discontinued and the patient treated with the usual agents (e.g. adrenaline or other pressor amines, antihistamines or corticosteroids).

Broad spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis. As with other broad spectrum antibiotics, colitis, including rare instances of pseudomembranous colitis, has been reported in conjunction with therapy with cephalexin.

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 diarrhoea in association with the use of antibiotics. Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, appropriate measures should be taken. 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 *Cl. difficile* should be considered. Fluids, electrolytes and protein replacement therapy should be provided when indicated. Drugs that delay peristalsis, e.g. opiates and diphenoxylate with atropine (e.g. Lomotil), may prolong and/or worsen the condition and should not be used.

Patients should be followed carefully so that any side effects or unusual manifestations of drug idiosyncrasy may be detected. If an allergic reaction to cephalexin occurs, the drug should be discontinued and the patient treated with the usual agents (e.g. adrenaline or other pressor amines, antihistamines or corticosteroids).

Prolonged use of cephalexin 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.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

### Impaired Renal Function

Cephalexin should be administered with caution in the presence of markedly impaired renal function. Careful clinical and laboratory studies should be made because safe dosage may be lower than that usually recommended.

### Use in Pregnancy (Category A)

Laboratory experiments with animals and clinical experience show no evidence of teratogenicity with cephalexin, but as with all drugs, cephalexin should be administered with caution during all stages of pregnancy.

*Category A: Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.*

### Use in Lactation

Cephalexin is excreted in the milk. Caution should be exercised when cephalexin is administered to a breastfeeding woman. Alternative feeding arrangements for the infant should be considered.

## INTERACTIONS WITH OTHER MEDICINES

### Probenecid

Probenecid decreases the renal tubular secretion of cephalexin resulting in increased and prolonged serum concentrations and increased elimination half life and consequently an increased risk of toxicity.

### Metformin

In healthy subjects given single 500 mg doses of cephalexin and metformin, plasma metformin  $C_{max}$  and AUC increased by an average of 34% and 24%, respectively, and metformin renal clearance decreased by an average of 14%. The interaction of cephalexin and metformin following multiple dose administration has not been studied. Administration of a cephalosporin to a metformin-treated patient may result in increased metformin exposure.

## Laboratory Tests

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. 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.

A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions or with Clinitest tablets, but not with urine sugar tape (Tes-Tape). The quantitative determination of urinary protein excretion using strong acids is misleading during cephalexin therapy as precipitation of cephalexin in the urine may occur.

## ADVERSE EFFECTS

Adverse drug reactions reported with cephalexin are very rare (<0.01%) and are listed below:

### **Central nervous system**

Dizziness, headache, agitation, confusion, hallucinations

### **Gastrointestinal Disorders**

Nausea, Vomiting, Diarrhoea, Dyspepsia, Abdominal Pain

### **General Disorders and Administration Site Conditions**

Fatigue

### **Blood and Lymphatic System Disorders**

Eosinophilia, neutropenia thrombocytopenia and haemolytic anaemia.

### **Hepatobiliary Disorders**

Cholestatic Jaundice, Transient Hepatitis, Elevated SGOT, Elevated SGPT.

### **Immune System Disorders**

Allergic Reactions, urticaria, angioedema and rarely, erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis have been observed. These reactions usually subsided upon discontinuation of the drug. Anaphylaxis has also been reported.

### **Infections and Infestations**

Pseudomembranous colitis

**Musculoskeletal and Connective Tissue Disorders**

Arthralgia, arthritis and joint disorders.

**Nervous System Disorders**

Dizziness, headache

**Psychiatric Disorders**

Hallucinations, agitation, confusion

**Renal and Urinary Disorders**

Reversible interstitial nephritis.

**Reproductive and Breast Disorders**

Genital and anal pruritus, genital moniliasis, vaginitis and vaginal discharge.

**Skin and Subcutaneous Tissue Disorders**

Rash, Erythema Multiforme, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis  
These reactions usually subsided upon discontinuation of the drug.

**DOSAGE AND ADMINISTRATION**

Administered orally.

**Adults**

The adult dosage ranges from 1 to 4 g daily in divided doses. The usual adult dose is 250 mg every six hours.

For streptococcal pharyngitis or tonsillitis, mild, uncomplicated urinary tract infections, and skin and skin structure infections, a dosage of 500 mg may be administered every twelve hours.

For more severe infections or those caused by less susceptible organisms, larger doses may be needed. If daily doses of cephalexin greater than 4 g are required, parenteral cephalosporins, in appropriate doses, should be considered.

Twice daily dosing is not recommended when doses larger than 1 g daily are administered.

**Children**

The usual recommended daily dosage for children is 25 to 50 mg/kg in divided doses. For streptococcal pharyngitis in patients over 1 year of age, tonsillitis, mild, uncomplicated urinary tract infection, and skin and skin structure infections, the total daily dose may be divided and administered every twelve hours.

<b>Part A: Four times daily dosage</b>		
<b>Child's Weight</b>	<b>Suspension 125 mg / 5 mL</b>	<b>Suspension 250 mg / 5 mL</b>
10 kg	2.5 to 5 mL 4 times daily	–
20 kg	5 to 10 mL 4 times daily	2.5 to 5 mL 4 times daily
40 kg	10 to 20 mL 4 times daily	5 to 10 mL 4 times daily

**Part B: Twice daily dosage**

<b>Child's Weight</b>	<b>Suspension 125 mg / 5 mL</b>	<b>Suspension 250 mg / 5 mL</b>
10 kg	5 to 10 mL twice daily	2.5 to 5 mL twice daily
20 kg	10 to 20 mL twice daily	5 to 10 mL twice daily
40 kg	20 to 40 mL twice daily	10 to 20 mL twice daily

In severe infections, the dosage may be doubled. In the therapy of otitis media, clinical studies have shown that a dosage of 75 to 100 mg/kg/day in four divided doses is recommended.

In the treatment of  $\beta$ -haemolytic streptococcal infections, a therapeutic dosage of cephalexin should be administered for at least 10 days.

**Impaired Renal Function:** see **PRECAUTIONS**

**OVERDOSAGE****Symptoms**

There is no definite experience of poisoning or severe overdosage with cephalexin. However, clinical features of overdosage may be similar to those seen with other cephalosporins and penicillins, i.e. convulsions, hallucinations, hyperreflexia, electrolyte imbalance, gastrointestinal disturbances and haematuria.

**Treatment**

In the event of severe overdosage, general supportive care is recommended including close clinical and laboratory monitoring of haematological, renal, hepatic functions and coagulation status until the patient is stable.

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

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

**PRESENTATION AND STORAGE CONDITIONS****APO-Cephalexin 125 mg/5 mL Powder for Suspension**

Pink coloured powder forming pink coloured suspension with characteristic odour on constitution.

Bottles of 100 mL.

AUST R 160864

**APO-Cephalexin 250 mg/5 mL Powder for Suspension**

Pink coloured powder forming pink coloured suspension with characteristic odour on constitution.

Bottles of 100 mL.

AUST R 160865.

APO-Cephalexin Powder for Suspension contains cephalexin (as monohydrate) equivalent to 125 mg/5mL or 250 mg/5mL of cephalexin anhydrous.

In addition, it contains the following inactive ingredients: Xanthan gum, sodium benzoate, allura red AC, colloidal anhydrous silica, sucrose, artificial strawberry flavour.

**Storage Before Mixing:** Store below 25°C. Protect from light and moisture.

**Storage After Mixing:** Store at 2 to 8°C. (Refrigerate. Do not freeze).

Discard unused portion after 14 days.

**NAME AND ADDRESS OF THE SPONSOR**

Apotex Pty Ltd  
16 Giffnock Avenue  
Macquarie Park NSW 2113

Apotex Pty Ltd is the licensee of the registered trade marks APO and APOTEX from the registered proprietor, Apotex Inc.

**POISON SCHEDULE OF THE MEDICINE**

S4: Prescription Only Medicine.

**Date of TGA approval:** 22 May 2009

**Date of most recent amendment:** 22 September 2012