AUSTRALIAN PRODUCT INFORMATION

KEFLOR®

(cefaclor (as monohydrate)) powder for oral suspension

1 NAME OF THE MEDICINE

Cefaclor monohydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle of KEFLOR 125 mg / 5mL powder for oral suspension upon reconstitution contains 125 mg of cefaclor (as monohydrate) as the active ingredient, per 5 mL of suspension.

Each bottle of KEFLOR 250 mg / 5mL powder for oral suspension upon reconstitution contains 250 mg of cefaclor (as monohydrate) as the active ingredient, per 5 mL of suspension.

Excipients with known effect: sugars.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

KEFLOR 125 mg/5 mL is a powder for oral suspension. The powder is a pink free-flowing dry powder. After reconstitution, it is a red coloured suspension with a characteristic strawberry odour.

KEFLOR 250 mg/5 mL is a powder for oral suspension. The powder is a pink free-flowing dry powder. After reconstitution, it is a red coloured suspension with a characteristic strawberry odour.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

KEFLOR is indicated for the treatment of the following types of infections caused by or likely to be caused by susceptible organisms:

- Lower respiratory infections, including pneumonia, bronchitis and exacerbations of chronic bronchitis.
- Upper respiratory 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. KEFLOR appears to be as effective as phenoxymethyl penicillin 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

KEFLOR is administered orally.

Directions for Reconstitution of KEFLOR for Oral Suspension

125 mg/5 mL - Add 60 mL of water in two portions to the dry mixture in the bottle. Shake well after each addition.

250 mg/5 mL - Add 45 mL of water in two portions to the dry mixture in the bottle. Shake well after each addition.

Reconstituted KEFLOR for Oral Suspension should be stored under refrigeration (2 - 8°C) and may be kept for 14 days without significant loss of potency.

Adults

The usual adult dosage is 250 mg every 8 to 12 hours. For bronchitis and pneumonia, the dosage is 250 mg administered 3 times daily. For more severe infections or those caused by less susceptible organisms, doses may be doubled (500 mg 8 hourly). Doses of 2 g/day should not be exceeded.

For skin and skin structure infections the dosage is 250 mg 2-3 times a day.

Children

The usual recommended daily dosage for children with mild to moderate infections is 20 mg/kg/day in divided doses every 8 hours (maximum 1 g/day).

For streptococcal pharyngitis/tonsillitis and impetigo, 12 hourly administration 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 8 to 12 hours (maximum 2 g/day). For otitis media, 12 hourly administration appears equally effective.

KEFLOR may be administered in the presence of impaired renal function. Under such a condition, the dosage usually is unchanged (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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

4.3 CONTRAINDICATIONS

KEFLOR 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) or any of the excipients.

KEFLOR is also contraindicated in infants under the age of one month as safety and efficacy of this product has not been established in prematures and infants under one month of age.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with antibiotic therapy in general, administration of KEFLOR 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 KEFLOR 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.

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

Allergic Reaction (Anaphylaxis)

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 KEFLOR. 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, KEFLOR should be discontinued and the appropriate therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with adrenaline (epinephrine). Oxygen, intravenous steroids and airway management, including intubation, should also be administered as indicated.

Risk-benefit should be considered when the following medical problems exist:

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.

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 hypoprothrombinemia and, potentially, bleeding.

Neurotoxicity

There have been reports of neurotoxicity associated with cephalosporin treatment. Symptoms of neurotoxicity include encephalopathy, seizures and/or myoclonus (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Risk factors for developing neurotoxicity with cephalosporin treatment include being elderly, renal impairment, central nervous system disorders and intravenous administration. Withdrawal of the medicine should be considered if there are signs of neurotoxicity.

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, KEFLOR should be discontinued immediately and an alternative treatment should be considered.

Use in Renal Impairment

Many cephalosporins are excreted renally. KEFLOR 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 Hepatic Impairment

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

Dental

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

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.

Paediatric Use

Safety and effectiveness of this product for use in infants less than one 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.

Effects on Laboratory Tests

Glucose, urine:

Administration of KEFLOR 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 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.

Prothrombin time (PT):

May be prolonged.

Creatinine, serum:

Concentrations may be increased.

Carnitine or Haematocrit:

Values may decrease during therapy.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Anticoagulants, 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

Hypoprothrombinemia induced by large doses of salicylates and/or cephalosporins, and the gastrointestinal ulcerative or haemorrhagic potential of nonsteroidal anti-inflammatory drugs (NSAIDs), salicylates, or sulfinpyrazone may increase the risk of haemorrhage.

Antacids

The extent of absorption of cefaclor is diminished if aluminium hydroxide-or magnesium-containing antacids are taken within 1 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Adequate and well-controlled studies in humans have not been done. However, studies in animals have not shown that cefaclor causes 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 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.

Use in Lactation

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 KEFLOR 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)

Gastrointestinal Disorders

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 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%).

Infections and Infestations

Genital pruritus, moniliasis or vaginitis.

Nervous System Disorders

Rare: reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, hallucinations, headache or somnolence have been reported.

Transitory abnormalities in clinical laboratory test results for hepatobiliary, blood and renal disorders have been reported, but their clinical significance is uncertain.

Hepatobiliary Disorders

Transient hepatitis and cholestatic jaundice have been reported rarely.

Slight elevations in AST, ALT, or alkaline phosphatase values have also been reported.

Blood and Lymphatic System Disorders

Eosinophilia, transient lymphocytosis, leukopenia, 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 leukocyte count, predominantly lymphocytosis in infants and young children.

Renal and Urinary Disorders

Reversible interstitial nephritis, slight elevations in serum urea or serum creatinine or abnormalities of urinalysis (haematuria; pyuria).

Skin and Other Subcutaneous Tissue Disorders

Severe cutaneous adverse reactions, including 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 beta-lactam antibiotics.

Post-marketing Experience

Nervous System Disorders

Frequency not known: seizures, encephalopathy and/or myoclonus.

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.

4.9 OVERDOSE

Signs and Symptoms

The toxic symptoms following an overdose of KEFLOR 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, 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.

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

KEFLOR (cefaclor monohydrate) is a semisynthetic cephalosporin antibiotic for oral administration.

Microbiology

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:

Staphylococci, including coagulase-positive and penicillinase-producing strains (but not methicillin-resistant strains of *Staph. aureus*).

- *Streptococcus pyogenes* (group A beta-haemolytic streptococci).
- *Streptococcus (Diplococcus) pneumoniae*
- *Escherichia coli*
- *Proteus mirabilis*
- *Klebsiella sp*
- *Haemophilus influenzae*
- *Neisseria gonorrhoeae* (penicillinase-producing and non-penicillinase producing strains).
- *Moraxella (branhamella) catarrhalis*

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

Susceptibility Testing

Dilution or Diffusion Techniques - either quantative (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 available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

KEFLOR 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 minutes to 1 hour 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.

Metabolism

There is no evidence of metabolism of cefaclor in humans.

Excretion

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Long-term studies in animals to evaluate the mutagenic potential of cefaclor have not been done.

Carcinogenicity

Long-term studies in animals to evaluate the carcinogenic potential of cefaclor have not been done.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sucrose, erythrosine, methylcellulose, sodium lauryl sulfate, Strawberry Flavour 52312 AP0551 (ARTG PI No: 274), dimeticone 350, xanthan gum and pregelatinised starch.

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

For the dry powder: Store below 25°C.

After reconstitution: The suspension should be stored under refrigeration (2 - 8°C) and may be kept for 14 days without significant loss of potency.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: (HDPE) bottle with child resistant/tamper evident screw cap

Pack sizes: 75 mL (250 mg/5 mL), 100 mL (125 mg/5 mL)

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 58651 - KEFLOR cefaclor 125mg/5mL (as monohydrate) powder for oral liquid bottle

AUST R 58653 - KEFLOR cefaclor 250mg/5mL (as monohydrate) powder for oral liquid bottle

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

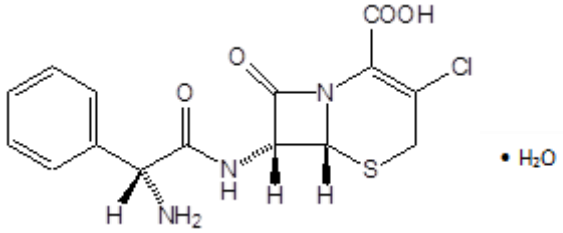
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

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

Structural formula :



Molecular formula : $C_{15}H_{14}ClN_3O_4S \cdot H_2O$

Molecular weight : 385.83

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

CAS Number

53994-73-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

19/02/1997

10 DATE OF REVISION

07/03/2024

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
4.4	Added warning of neurotoxicity.
4.8	Added adverse effects of nervous system disorders in section of post-marketing experience.

KEFLOR® is a Viatris company trade mark

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