

KEFLEX[®]

Cephalexin oral suspension, USP

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KEFLEX[®] safely and effectively. See full prescribing information for KEFLEX[®]

KEFLEX[®] (cephalexin) oral suspension
Initial U.S. Approval: 1971

INDICATIONS AND USAGE

KEFLEX is a cephalosporin antibacterial drug indicated for the treatment of the following infections caused by susceptible isolates of designated bacteria:

- Respiratory tract infection (1.1)
- Otitis media (1.2)
- Skin and skin structure infections (1.3)
- Bone infections (1.4)
- Genitourinary tract infections (1.5)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of KEFLEX and other antibacterial drugs, KEFLEX should be used only to treat infections that are proven or strongly suspected to be caused by bacteria. (1.6)

DOSAGE AND ADMINISTRATION

Adults and patients at least 15 years of age	The usual dose is 250 mg every 6 hours, but a dose of 500 mg every 12 hours may be administered (2.1).
Pediatric patients (over 1 year of age)	<ul style="list-style-type: none">• Otitis media: 75 to 100 mg/kg in equally divided doses every 6 hours (2.2)• All other indications: 25 to 50 mg/kg given in equally divided doses (2.2)• In severe infections: 50 to 100 mg/kg may be administered in equally divided doses (2.2)

- Duration of therapy ranges from 7 to 14 days depending on the infection type and severity. (2)
- Dosage adjustment is required in patients with severe and end stage renal disease (ESRD) defined as creatinine clearance below 30 mL/min. (2.3)

DOSAGE FORMS AND STRENGTHS

For oral suspension: 125mg/5mL and 250mg/5mL (3)

CONTRAINDICATIONS

Patients with known hypersensitivity to cephalexin or other members of the cephalosporin class of antibacterial drugs. (4)

WARNINGS AND PRECAUTIONS

- **Serious hypersensitivity (anaphylactic) reactions:** Prior to use, inquire regarding history of hypersensitivity to beta-lactam antibacterial drugs. Discontinue the drug if signs or symptoms of an allergic reaction occur and institute supportive measures. (5.1)
- **Clostridium difficile-associated diarrhea (CDAD):** Evaluate if diarrhea occurs. (5.2)
- **Direct Coomb's Test Seroconversion:** If anemia develops during or after cephalexin therapy, evaluate for drug-induced hemolytic anemia. (5.3)
- **Seizure Potential:** Use lower dose in patients with renal impairment. (5.4)

ADVERSE REACTIONS

The most common adverse reactions associated with KEFLEX include diarrhea, nausea, vomiting, dyspepsia and abdominal pain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Pragma Pharmaceuticals, LLC at (414) 434-6604 Monday-Friday 9am-5pm EST, or to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Metformin: increased metformin concentrations. Monitor for hypoglycemia. (7.1)
- Probenecid - The renal excretion of KEFLEX is inhibited by probenecid. Co-administration of probenecid with KEFLEX is not recommended. (7.2)
- Administration of KEFLEX may result in a false-positive reaction for glucose in the urine. (7.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2018

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FULL PRESCRIBING INFORMATION**1. INDICATIONS AND USAGE****1.1 Respiratory Tract Infections**

KEFLEX is indicated for the treatment of respiratory tract infections caused by susceptible isolates of *Streptococcus pneumoniae* and *Streptococcus pyogenes*.

1.2 Otitis Media

KEFLEX is indicated for the treatment of otitis media caused by susceptible isolates of *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Moraxella catarrhalis*.

1.3 Skin and Skin Structure Infections

KEFLEX is indicated for the treatment of skin and skin structure infections caused by susceptible isolates of the following Gram-positive bacteria: *Staphylococcus aureus* and *Streptococcus pyogenes*.

1.4 Bone Infections

KEFLEX is indicated for the treatment of bone infections caused by susceptible isolates of *Staphylococcus aureus* and *Proteus mirabilis*.

1.5 Genitourinary Tract Infections

KEFLEX is indicated for the treatment of genitourinary tract infections, including acute prostatitis, caused by susceptible isolates of *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella pneumoniae*.

1.6 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of KEFLEX and other antibacterial drugs, KEFLEX should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information is available, this information should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2. DOSAGE AND ADMINISTRATION

2.1 Adults and Pediatric Patients at Least 15 Years of Age

The usual dose of oral KEFLEX is 250 mg every 6 hours, but a dose of 500 mg every 12 hours may be administered. Treatment is administered for 7 to 14 days.

For more severe infections larger doses of oral KEFLEX may be needed, up to 4 grams daily in two to four equally divided doses.

2.2 Pediatric Patients (over 1 year of age)

The recommended total daily dose of oral KEFLEX for pediatric patients is 25 to 50 mg/kg given in equally divided doses for 7 to 14 days. In the treatment of β -hemolytic streptococcal infections, duration of at least 10 days is recommended. In severe infections, a total daily dose of 50 to 100 mg/kg may be administered in equally divided doses.

For the treatment of otitis media, the recommended daily dose is 75 to 100 mg/kg given in equally divided doses.

	Keflex Suspension	
<u>Weight</u>	<u>125mg/5mL</u>	<u>250mg/5mL</u>
10 kg (22 lb)	½ to 1 tsp q.i.d.	¼ to ½ tsp q.i.d.
20 kg (44 lb)	1 to 2 tsp q.i.d.	½ to 1 tsp q.i.d.
40 kg (88 lb)	2 to 4 tsp q.i.d.	1 to 2 tsp q.i.d.
	Or	
<u>Weight</u>	<u>125mg/5mL</u>	<u>250mg/5mL</u>
10 kg (22 lb)	1 to 2 tsp b.i.d.	½ to 1 tsp b.i.d.
20 kg (44 lb)	2 to 4 tsp b.i.d.	1 to 2 tsp b.i.d.
40 kg (88 lb)	4 to 8 tsp b.i.d.	2 to 4 tsp b.i.d.

Directions for Mixing

125 mg per 5 mL (100 mL when mixed): Prepare suspension time at dispensing. Add to the bottle a total of 71 mL of water. For ease in preparation, tap bottle to loosen powder, add the water in 2 portions, shaking well after each addition. The resulting suspension will contain cephalexin monohydrate equivalent to 125 mg cephalexin in each 5 mL (teaspoonful).

125 mg per 5 mL (200 mL when mixed): Prepare suspension time at dispensing. Add to the bottle a total of 140 mL of water. For ease in preparation, tap bottle to loosen powder, add the water in 2 portions, shaking well after each addition. The resulting suspension will contain cephalexin monohydrate equivalent to 125 mg cephalexin in each 5 mL (teaspoonful).

250 mg per 5 mL (100 mL when mixed): Prepare suspension time at dispensing. Add to the bottle a total of 71 mL of water. For ease in preparation, tap bottle to loosen powder, add the water in 2 portions, shaking well after each addition. The resulting suspension will contain cephalexin monohydrate equivalent to 250 mg cephalexin in each 5 mL (teaspoonful).

250 mg per 5 mL (200 mL when mixed): Prepare suspension time at dispensing. Add to the bottle a total of 140 mL of water. For ease in preparation, tap bottle to loosen powder, add the water in 2 portions, shaking well after each addition. The resulting suspension will contain cephalexin monohydrate equivalent to 250 mg cephalexin in each 5 mL (teaspoonful).

*After mixing, store in refrigerator. May be kept for 14 days without significant loss of potency.

2.3 Dosage Adjustments in Adult and Pediatric Patients at Least 15 Years of Age with Renal Impairment

Administer the following dosing regimens for KEFLEX to patients with impaired renal function [*see Warnings and Precautions (5.4) and Use in Specific Populations (8.6)*].

Table 1. Recommended Dose Regimen for Patients with Renal Impairment

Renal function	Dose regimen recommendation
Creatinine clearance \geq 60 mL/min	No dose adjustment
Creatinine clearance 30 to 59 mL/min	No dose adjustment; maximum daily dose should not exceed 1 g
Creatinine clearance 15 to 29 mL/min	250 mg, every 8 hours or every 12 hours
Creatinine clearance 5 to 14 mL/min not yet on dialysis*	250 mg, every 24 hours
Creatinine clearance 1 to 4 mL/min not yet on dialysis*	250 mg, every 48 hours or every 60 hours

*There is insufficient information to make dose adjustment recommendations in patients on hemodialysis.

3. DOSAGE FORMS AND STRENGTHS

KEFLEX for oral suspension USP

125 mg/5mL and 250 mg/5mL

4. CONTRAINDICATIONS

KEFLEX is contraindicated in patients with known hypersensitivity to cephalexin or other members of the cephalosporin class of antibacterial drugs.

5. WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Allergic reactions in the form of rash, urticaria, angioedema, anaphylaxis, erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis have been reported with the use of KEFLEX. Before therapy with KEFLEX is instituted, inquire whether the patient has a history of hypersensitivity reactions to cephalexin, cephalosporins, penicillins, or other drugs. Cross-hypersensitivity among beta-lactam antibacterial drugs may occur in up to 10% of patients with a history of penicillin allergy.

If an allergic reaction to KEFLEX occurs, discontinue the drug and institute appropriate treatment.

5.2 *Clostridium difficile*-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including KEFLEX, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.3 Direct Coombs' Test Seroconversion

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibacterial drugs including cephalexin. Acute intravascular hemolysis induced by cephalexin therapy has been reported. If anemia develops during or after cephalexin therapy, perform a diagnostic work-up for drug-induced hemolytic anemia, discontinue cephalexin and institute appropriate therapy.

5.4 Seizure Potential

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. If seizures occur, discontinue KEFLEX. Anticonvulsant therapy can be given if clinically indicated.

5.5 Prolonged Prothrombin Time

Cephalosporins may be associated with prolonged prothrombin time. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antibacterial therapy, and patients receiving anticoagulant therapy. Monitor prothrombin time in patients at risk and manage as indicated.

5.6 Development of Drug-Resistant Bacteria

Prescribing KEFLEX in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Prolonged use of KEFLEX 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.

6. ADVERSE REACTIONS

The following serious events are described in greater detail in the Warning and Precautions section:

- Hypersensitivity reactions [*see Warning and Precautions (5.1)*]
- *Clostridium difficile*-associated diarrhea [*see Warnings and Precautions (5.2)*]
- Direct Coombs' Test Seroconversion [*see Warnings and Precautions (5.3)*]
- Seizure Potential [*see Warnings and Precautions (5.4)*]
- Effect on Prothrombin Activity [*see Warnings and Precautions (5.5)*]
- Development of Drug-Resistant Bacteria [*see Warnings and Precautions (5.6)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, the most frequent adverse reaction was diarrhea. Nausea and vomiting, dyspepsia, gastritis, and abdominal pain have also occurred. As with penicillins and other cephalosporins, transient hepatitis and cholestatic jaundice have been reported.

Other reactions have included hypersensitivity reactions, genital and anal pruritus, genital candidiasis, vaginitis and vaginal discharge, dizziness, fatigue, headache, agitation, confusion, hallucinations, arthralgia, arthritis, and joint disorder. Reversible interstitial nephritis has been reported. Eosinophilia, neutropenia, thrombocytopenia, hemolytic anemia, and slight elevations in aspartate transaminase (AST) and alanine transaminase (ALT) have been reported.

In addition to the adverse reactions listed above that have been observed in patients treated with KEFLEX, the following adverse reactions and other altered laboratory tests have been reported for cephalosporin class antibacterial drugs:

Other Adverse Reactions: Fever, colitis, aplastic anemia, hemorrhage, renal dysfunction, and toxic nephropathy.

Altered Laboratory Tests: Prolonged prothrombin time, increased blood urea nitrogen (BUN), increased creatinine, elevated alkaline phosphatase, elevated bilirubin, elevated lactate dehydrogenase (LDH), pancytopenia, leukopenia, and agranulocytosis.

7. DRUG INTERACTIONS

7.1 Metformin

Administration of KEFLEX with metformin results in increased plasma metformin concentrations and decreased renal clearance of metformin.

Careful patient monitoring and dose adjustment of metformin is recommended in patients concomitantly taking KEFLEX and metformin [*see Clinical Pharmacology (12.2)*].

7.2 Probenecid

The renal excretion of KEFLEX is inhibited by probenecid. Co-administration of probenecid with KEFLEX is not recommended.

7.3 Interaction with Laboratory or Diagnostic Testing

A false-positive reaction may occur when testing for the presence of glucose in the urine using Benedict's solution or Fehling's solution.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are 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.

Reproduction studies have been performed on mice and rats using oral doses of cephalexin monohydrate 0.6 and 1.5 times the maximum daily human dose (66 mg/kg/day) based upon body surface area basis, and have revealed no evidence of impaired fertility or harm to the fetus.

8.3 Nursing Mothers

Cephalexin is excreted in human milk. Caution should be exercised when KEFLEX is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of KEFLEX in pediatric patients was established in clinical trials for the dosages described in the dosage and administration section [*see Dosage and Administration (2.2)*].

8.5 Geriatric Use

Of the 701 subjects in 3 published clinical studies of cephalexin, 433 (62%) were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

This drug is substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection [*see Warnings and Precautions (5.4)*].

8.6 Renal Impairment

KEFLEX should be administered with caution in the presence of impaired renal function (creatinine clearance < 30 mL/min, with or without dialysis). Under such conditions, careful clinical observation and laboratory studies renal function monitoring should be conducted because safe dosage may be lower than that usually recommended [*see Dosage and Administration (2.3)*].

10. OVERDOSAGE

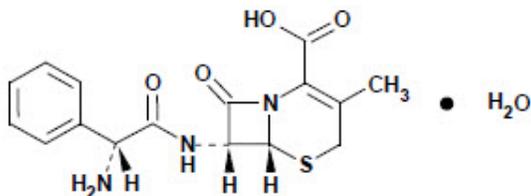
Symptoms of oral overdose may include nausea, vomiting, epigastric distress, diarrhea, and hematuria. In the event of an overdose, institute general supportive measures.

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

11. DESCRIPTION

KEFLEX® (cephalexin) oral suspension, USP is a semisynthetic cephalosporin antibacterial drug intended for oral administration. It is 7-(D- α -Amino- α -phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid monohydrate. Cephalexin has the molecular formula $C_{16}H_{17}N_3O_4S \cdot H_2O$ and the molecular weight is 365.41.

Cephalexin has the following structural formula:



Inactive Ingredients: SUSPENSION: The suspensions also contain flavors, methylcellulose, silicone, sodium lauryl sulfate, and sucrose. The 125-mg suspension contains FD&C Red No. 40, and the 250-mg suspension contains FD&C Yellow No. 6.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cephalexin is a cephalosporin antibacterial drug [*see Microbiology (12.4)*].

12.3 Pharmacokinetics

Absorption:

Cephalexin is acid stable and may be given without regard to meals. Following doses of 250 mg, 500 mg, and 1 g, average peak serum levels of approximately 9, 18, and 32 mcg/mL, respectively, were obtained at 1 hour. Serum levels were detectable 6 hours after administration (at a level of detection of 0.2 mcg/mL).

Distribution:

Cephalexin is approximately 10% to 15% bound to plasma proteins.

Excretion:

Cephalexin is excreted in the urine by glomerular filtration and tubular secretion. Studies showed that over 90% of the drug was excreted unchanged in the urine within 8 hours. During this period, peak urine concentrations following the 250 mg, 500 mg, and 1 g doses were approximately 1000, 2200, and 5000 mcg/mL respectively.

Drug Interactions:

In healthy subjects given single 500 mg doses of cephalexin and metformin, plasma metformin mean C_{max} and AUC increased by an average of 34% and 24%, respectively, and metformin mean renal clearance decreased by 14%. No information is available about the interaction of cephalexin and metformin following multiple doses of either drug.

12.4 Microbiology

Mechanism of Action

Cephalexin is a bactericidal agent that acts by the inhibition of bacterial cell-wall synthesis.

Resistance

Methicillin-resistant staphylococci and most isolates of enterococci are resistant to cephalexin. Cephalexin is not active against most isolates of *Enterobacter spp.*, *Morganella morganii*, and *Proteus vulgaris*. Cephalexin has no activity against *Pseudomonas spp.*, or *Acinetobacter calcoaceticus*. Penicillin-resistant *Streptococcus pneumoniae* is usually cross-resistant to beta-lactam antibacterial drugs.

Antimicrobial Activity

Cephalexin has been shown to be active against most isolates of the following bacteria both *in vitro* and in clinical infections [*see Indications and Usage (1)*].

Gram-positive bacteria

Staphylococcus aureus (methicillin-susceptible isolates only)

Streptococcus pneumoniae (penicillin-susceptible isolates)

Streptococcus pyogenes

Gram-negative bacteria

Escherichia coli

Haemophilus influenzae

Klebsiella pneumoniae

Moraxella catarrhalis

Proteus mirabilis

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: <https://www.fda.gov/STIC>.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifetime studies in animals have not been performed to evaluate the carcinogenic potential of cephalexin. Tests to determine the mutagenic potential of cephalexin have not been performed. In male and female rats, fertility and reproductive performance were not affected by cephalexin oral doses up to 1.5 times the highest recommended human dose based upon body surface area.

16. HOW SUPPLIED/STORAGE AND HANDLING

KEFLEX® for oral suspension, USP, is supplied as follows:

The 125 mg per 5 mL oral suspension* is available as follows:

- 100-mL Bottles NDC 58463-018-01 (PBL-01801)
- 200-mL Bottles NDC 58463-018-02 (PBL-01802)

The 250 mg per 5 mL oral suspension* is available as follows:

- 100-mL Bottles NDC 58463-019-01 (PBL-01901)
- 200-mL Bottles NDC 58463-019-02 (PBL-01902)

Directions for mixing are included on the label.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Shake well before using. Keep tightly closed.

*After mixing, store in refrigerator. May be kept for 14 days without significant loss of potency.

17. PATIENT COUNSELING INFORMATION

- Advise patients that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate treatment. Ask the patient about any previous hypersensitivity reactions to KEFLEX, other beta-lactams (including cephalosporins) or other allergens (5.1)
- Advise patients that diarrhea is a common problem caused by antibacterial drugs and usually resolves when the drug is discontinued. Sometimes, frequent watery or bloody diarrhea may occur and may be a sign of a more serious intestinal infection. If severe watery or bloody diarrhea develops, advise patients to contact their healthcare provider.
- Counsel patients that antibacterial drugs including KEFLEX, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When KEFLEX is prescribed to treat a bacterial infection, tell patients that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by KEFLEX or other antibacterial drugs in the future.

Manufactured in Austria for:

Pragma Pharmaceuticals, LLC

Distributed by: Fera Pharmaceuticals, LLC

Locust Valley, N.Y. 11560

Pragma™

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