KEFLEX- cephalexin capsule
DIRECT RX

CEPHALEXIN

1.1 Respiratory Tract Infections

Cephalexin capsules are indicated for the treatment of respiratory tract infections caused by susceptible isolates of Streptococcus pneumoniae and Streptococcus pyogenes.

1.2 Otitis Media

Cephalexin capsules are 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

Cephalexin capsules are 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

Cephalexin capsules are indicated for the treatment of bone infections caused by susceptible isolates of Staphylococcus aureus and Proteus mirabilis.

1.5 Genitourinary Tract Infections

Cephalexin capsules are 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 cephalexin capsules and other antibacterial drugs, cephalexin capsules 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.

2.1 Adults and Pediatric Patients At Least 15 years of age

The usual dose of oral cephalexin capsules 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 cephalexin capsules 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 cephalexin capsules 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.

2.3 Dosage Adjustments in Adult and Pediatric Patients At Least 15 years of Age with Renal Impairment

Administer the following dosing regimens for cephalexin capsules 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 *There is insufficient information to make dose adjustment recommendations in patients on hemodialysis.
Renal function
Dose regimen recommendation
Creatinine clearance ≥ 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

250 mg capsules: Dark green opaque/white size “2” hard gelatin capsule filled with off white granular powder and imprinted with “A 42” on dark green opaque cap and “250 mg” on white body with black ink.

500 mg capsules: Dark green opaque/light green opaque size “0” hard gelatin capsule filled with off white granular powder and imprinted with “A 43” on dark green opaque cap and “500 mg” on light green opaque body with black ink.

Cephalexin capsules are contraindicated in patients with known hypersensitivity to cephalexin or other members of the cephalosporin class of antibacterial drugs.

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 cephalexin. Before therapy with cephalexin 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 cephalexin 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 cephalexin, 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 cephalexin. 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 cephalexin 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 cephalexin 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.

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 cephalexin, 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.

7.1 Metformin

Administration of cephalexin 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 cephalexin and metformin [see Clinical Pharmacology (12.3)].

7.2 Probenecid

The renal excretion of cephalexin is inhibited by probenecid. Co-administration of probenecid with cephalexin 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.

8.1 Pregnancy

Teratogenic effects

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 cephalexin is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of cephalexin 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

Cephalexin 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)].

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.

Cephalexin capsules, 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 C16H17N3O4S•H2O and the molecular weight is 365.41.

Cephalexin has the following structural formula:

Chemical Structure

Each capsule contains cephalexin monohydrate equivalent to 250 mg or 500 mg of cephalexin. The capsules also contain the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, D&C Yellow No. 10, FD&C Blue No. 1, FD&C Yellow No. 6, gelatin, magnesium stearate, titanium dioxide, and sodium lauryl sulfate.

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 Cmax 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 Tests Methods

When available, the clinical microbiology laboratory should provide the results of in vitro susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

In cases of uncomplicated urinary tract infection only, susceptibility of E. coli, K. pneumoniae, and P. mirabilis to cephalexin may be inferred by testing cefazolin2 .

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test methods (broth or agar)1,2.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method2,3.

A report of Susceptible (S) indicates that the antimicrobial drug is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the site of infection. A report of Intermediate (I) 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 a high dosage of the drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of Resistant (R) indicates that the antimicrobial drug is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentrations usually achievable at the infection site; other therapy should be selected.

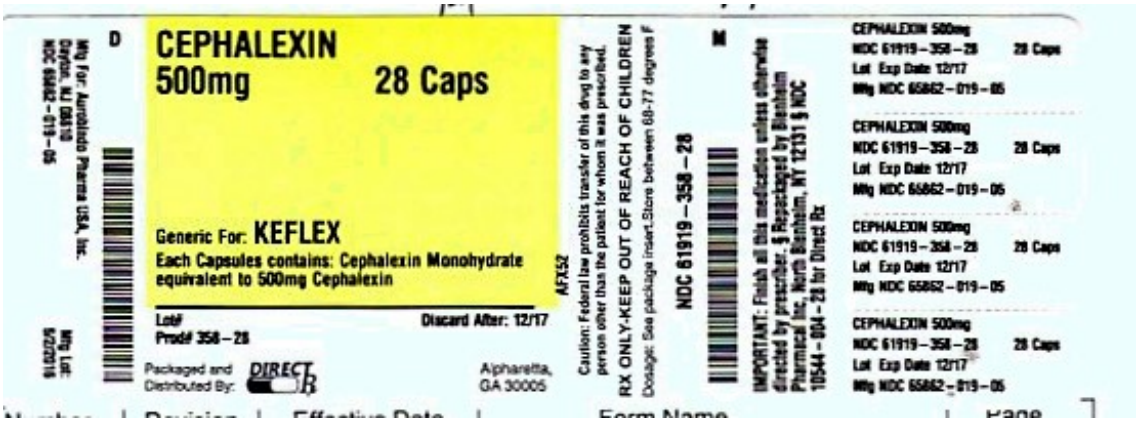
Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individual performing the test1,2,3,.

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.

Dark green opaque/light green opaque size “0” hard gelatin capsule filled with off white granular powder and imprinted with “A 43” on dark green opaque cap and “500 mg” on light green opaque body with black ink.



KEFLEX

cephalexin capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:61919-358(NDC:65862-019)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CEPHALEXIN (UNII: OBN7UDS42Y) (CEPHALEXIN ANHYDROUS - UNII:5SFF1W6677)	CEPHALEXIN ANHYDROUS	500 mg

Inactive Ingredients	
Ingredient Name	**Strength**
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
GELATIN (UNII: 2G86QN327L)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	

Product Characteristics			
Color	green (GREEN (Dark Green Opaque, Light Green Opaque))	**Score**	score with uneven pieces
Shape	CAPSULE	**Size**	21mm
Flavor		**Imprint Code**	A;43;500;mg
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61919-358-28	28 in 1 BOTTLE; Type 0: Not a Combination Product	05/02/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA065253	05/02/2016	

Labeler - DIRECT RX (079254320)

Establishment

Name	Address	ID/FEI	Business Operations
DIRECT RX		079254320	repack(61919-358)

Revised: 5/2016 DIRECT RX