Cefalexin

Cefalin®

250 mg Capsule
500 mg Capsule
Antibacterial

Rx

FORMULATIONS
Each capsule contains:
Cefalexin (as monohydrate) ..... 250 mg or 500 mg

PRODUCT DESCRIPTIONS
Cefalexin (Cefalin) 250 mg capsule is a glossy capsule (No.1) with maroon cap and faint gray body.
Cefalexin (Cefalin) 500 mg capsule is a glossy capsule (No.0) with maroon cap and body.

PHARMACODYNAMICS
Cefalexin is a semi-synthetic, first generation cephalosporin which exerts its bactericidal activity by interfering with the bacterial cell wall synthesis. It binds to specific penicillin-binding proteins responsible for the synthesis of peptidoglycan, a heteropolymeric structure that gives the cell wall its mechanical stability. The final stage of peptidoglycan synthesis involves completion of the cross-linking of the terminal glycine residue of the pentaglycine bridge to the fourth residue of the pentapeptide. The transpeptidase enzyme that catalyzes this step is inhibited by cephalosporins. As a result the bacterial cell wall is weakened, the cell swells and then ruptures.

ANTIMICROBIAL SPECTRUM OF ACTIVITY
Cefalexin is active *in vitro* and in clinical infections against most strains of the following microorganisms:

Aerobic Gram-positive	Aerobic Gram-negative
Staphylococcus aureus (including penicillinase-producing strains) *Staphylococcus epidermidis* (penicillin-susceptible strains) *Streptococcus pneumoniae* (penicillin-susceptible strains) *Streptococcus pyogenes*	*Escherichia coli* *Haemophilus influenzae* *Klebsiella pneumoniae* *Moraxella catarrhalis* *Proteus mirabilis*

Cefalexin is inactive against methicillin-resistant staphylococci and most strains of enterococci (e.g., *Enterococcus faecalis*), *Enterobacter* spp., *Morganella morganii*, and *Proteus vulgaris*. It has no activity against *Pseudomonas* spp. or *Acinetobacter calcoaceticus*. Penicillin-resistant *Streptococcus pneumoniae* is usually cross-resistant to beta-lactam antibiotics.

It is suggested to carry out susceptibility tests.

PHARMACOKINETICS
Cefalexin is acid stable and is rapidly and completely absorbed from the gastrointestinal (GI) tract. After single oral doses of cefalexin 250 mg and 500 mg in healthy, fasting adults with normal renal function, the mean peak serum concentrations (C_{max}) are 9 and 18 mcg/mL, respectively, and are achieved within one hour of administration. Serum concentrations are still detectable after 6 hours.

When cefalexin is administered with food, the peak serum concentrations are slightly lower and are attained later, although the total amount of drug absorbed remains unchanged.

Cefalexin readily diffuses into tissues, including bone, joints and the pericardial as well as pleural cavities. It reaches therapeutic levels in the blood, urine, bile, synovial fluid, pus, tonsillar tissue, amniotic fluid, cord blood, and fetal blood. Cefalexin does not enter the cerebrospinal fluid (CSF) in significant quantities. The drug crosses the placenta and small quantities are found in breast milk.

The serum half-life ($t_{1/2}$) of cefalexin is 0.5 to 1.2 hours in adults with normal renal function. In adults with creatinine clearances of 13.5, 9.2 and 4 mL/minute, the serum $t_{1/2}$ were 7.7, 10.8, and 13.9, respectively.

Cefalexin is not metabolized in the body. It is excreted unchanged in the urine by both glomerular filtration and tubular secretion. About 70-90% of a single oral dose of cefalexin 250- or 500 mg is excreted within 8-12 hours in adults with normal renal function. Peak urine concentrations average about 2 mg/mL and occur 2 hours after a single 500 mg oral dose of cefalexin.

INDICATIONS
For the treatment of the following infections caused by susceptible microorganisms:
- Skin and skin structure infections
- Bone and joint infections
- Genitourinary tract infections, including acute prostatitis
- Respiratory tract infections including acute and chronic bronchitis and infected bronchiectasis
- Ear, nose and throat infections including otitis media, mastoiditis, sinusitis, follicular tonsillitis, and pharyngitis
- Dental infections

Note: Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Cefalexin is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of cefalexin in the subsequent prevention of rheumatic fever are not available at present.

DOSAGE AND ADMINISTRATION
Cefalexin is administered orally.

Usual Adult Dose: 250 mg every 6 hours (Maximum Dose: 4 g/day)
- For streptococcal pharyngitis, skin and skin structure infections and uncomplicated cystitis (in patients > 15 years old): 500 mg every 12 hours
- Larger doses (up to 4 g daily) may be needed for more severe infections or those caused by less susceptible organisms. If daily doses of cefalexin greater than 4 g are required, initial therapy with parenteral cephalosporins, in appropriate doses, should be considered.

Elderly: Follow the usual adult dose. However, dosage should be reduced in case of renal impairment.

Patients with Renal Impairment: The initial dose is the same as in patients with normal renal function.

Subsequent doses are based on the patient's creatinine clearance as shown below:

Recommended Maintenance Dose in Adults with Renal Impairement

Creatinine clearance (mL/min)	Unit Dose of Cefalexin	Frequency
11-40	500 mg	Every 8-12 hours
5-10	250 mg	Every 12 hours
< 5	250 mg	Every 12-24 hours

Adult patients receiving intermittent dialysis should be given an additional 500 mg of cefalexin after each dialysis, i.e. a total dosage of up to 1 g on that day.

Usual Duration of Treatment:
- **For mild to moderate infections:** 5 to 7 days
- **For cystitis:** 7 to 14 days
- **For ß-hemolytic streptococcal infections:** At least 10 days

Or, as prescribed by a physician.

CONTRAINDICATIONS
Known hypersensitivity to cephalosporins, penicillins, or any component of the product.

WARNINGS AND PRECAUTIONS
- **Careful inquiry should be made prior to cefalexin therapy to determine whether the patient has had previous hypersensitivity reactions to cefalexin, cephalosporins, penicillins, or other drugs. Use with caution in penicillin-sensitive patients since cross-sensitivity among ß-lactam antibiotics has been clearly documented and may occur in up to 10% of patients with a history of allergy to penicillin. In case of an allergic reaction to cefalexin, the drug should be discontinued. Serious acute hypersensitivity reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous antihistamines, corticosteroids, and airway management, including intubation, should also be instituted.**
- Clostridium difficile-associated diarrhea (CDAD) and colitis have been reported with nearly all antibacterial agents, including cefalexin, and may range in severity from mild to life threatening. It is important to consider this diagnosis in patients who present with diarrhea after administration of antibacterial agents.
- Seizures have been reported with several cephalosporins (e.g., ceftazidime, cefuroxime), particularly in patients with impaired renal function in whom dosage of the drug was not reduced. If seizures occur during treatment with cephalosporin, the drug should be discontinued and anticonvulsant therapy initiated as clinically indicated.
- Cephalosporins may be associated with a fall in prothrombin activity particularly in patients with renal or hepatic impairment, or poor nutritional state, as well as those receiving a protracted course of antibiotic therapy, and patients stabilized on anticoagulants. Monitoring of prothrombin time in patients at risk and exogenous vitamin K administration are recommended.

- A false-positive Coombs' test has been reported during treatment with other cephalosporin antibiotics; therefore, it should be recognized that a positive Coombs' test may be due to the drug, e.g., Coombs' testing of newborns whose mothers have received cephalosporins before parturition or in hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed.
- Use with caution in patients with renal impairment. Careful clinical and laboratory studies should be made since safe dosage may be lower than that usually recommended.
- Indicated surgical procedures (e.g., incision and drainage of abscesses) should be performed in conjunction with antibiotic therapy.
- As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, hematopoietic, is recommended during prolonged therapy.
- Prescribing cefalexin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.
- As with other antibacterial drugs, long term or repeated use may result in overgrowth of non-susceptible organisms, including fungi.

INTERACTIONS WITH OTHER MEDICAMENTS

No potentially hazardous interactions have been reported. However, it may share the interaction potential of other cephalosporins as with the following:

- **Alcohol:** Disulfiram-like reactions have occurred when alcohol was ingested within 48 to 72 hours after administration of ß-lactam antibiotics that contain N-methylthiotetrazole side chain. The reactions appear to result from accumulation of acetaldehyde and do not occur if alcohol is ingested prior to the first dose of antibiotic. Ingestion of alcohol during and for 24 to 72 hours after administration of some cephalosporins should be avoided.
- **Probenecid:** Concomitant administration of oral probenecid competitively inhibits tubular secretion resulting in higher and more prolonged serum concentrations of most cephalosporins.
- **Estrogens or Progestins:** Some cephalosporins (e.g., ceftazidime) may affect gut flora, leading to lower estrogen reabsorption and reduced efficacy of oral contraceptives.
- **Metformin:** When single 500 mg doses of cefalexin and metformin were given to 12 healthy subjects, plasma metformin C_{max} and AUC increased by an average of 34% and 24%, respectively, and metformin's renal clearance decreased by an average of 14%. Information on the interaction of cefalexin and metformin after multiple dose administration is unavailable. Careful patient monitoring and metformin dose adjustment is recommended during concomitant therapy.
- **Nephrotoxic Drugs:** Concurrent use of nephrotoxic agents such as aminoglycosides, colistin, polymyxin B, or vancomycin may increase the risk of nephrotoxicity with some cephalosporins and probably should be avoided, if possible.
- **Diuretics:** Concurrent treatment with high doses of cephalosporins and potent diuretics (e.g., furosemide) may adversely affect renal function.
- **Other Anti-infective Agents:** *In vitro* studies indicate that the antibacterial activity of cephalosporins against some organisms may be additive or synergistic with aminoglycosides and penicillins. Although some in vitro studies showed additive or synergistic antibacterial activity between chloramphenicol and a cephalosporin, there is more recent *in vitro* evidence of antagonism between cephalosporins and chloramphenicol against a variety of Gram-negative and Gram-positive bacteria, particularly when chloramphenicol was added to the medium before the ß-lactam. In addition, at least one case of *in vivo* antagonism has been reported in an infant with *Salmonella enteritidis* meningitis. Therefore, it is recommended that combined therapy with chloramphenicol and a cephalosporin be avoided, particularly when bactericidal activity is considered important.

Interference with Laboratory Tests:

- Cefalexin capsules may cause false-positive glucose reaction in urine with Benedict's and Fehling's solutions and Clinitest® tablets.
- A false-positive direct Coombs' test has been reported during treatment with other cephalosporin antibiotics; therefore it should be recognized that a positive Coombs' test may be due to the drug.
- Cefalexin can interfere with the alkaline picrate assay for creatinine, giving a falsely high reading, although the degree of elevation is unlikely to be of clinical importance.
- The quantitative determination of urinary protein excretion using strong acids is misleading during cefalexin therapy as precipitation of cefalexin in the urine may occur.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy: (Pregnancy Category B). Reproduction studies have been performed in mice and rats using oral doses of cefalexin monohydrate 6 and 1.5 times the maximum daily human dose based upon mg/m², and have revealed no harmful effects to the fetus. However, there are no adequate and well-controlled studies in pregnant women. Since animal reproduction studies are not always predictive of human response, cefalexin should be used only if clearly needed.

Lactation: The excretion of cefalexin in human milk increased up to 4 hours after a 500 mg dose; the drug reached a maximum level of 4 mcg/mL, then decreased gradually, and had disappeared 8 hours after administration. Cefalexin should be used with caution during breastfeeding.

Renal Impairment: In patients with impaired renal function, decreases in doses and/or frequency of administration of cefalexin may be required and should be based on the degree of renal impairment, severity of infection, susceptibility of the causative organism, and serum concentrations of cefalexin.

UNDESIRABLE EFFECTS

GI: Abdominal cramp/pain, anorexia, (e.g., oral thrush), CDAD and colitis, diarrhea, dyspepsia, gastritis, gastroenteritis, glossitis/stomatitis, nausea, vomiting

Dermatologic / Hypersensitivity Reactions: Anaphylaxis, angioedema, eosinophilia, erythema multiforme, fever, genital and anal pruritus, intertrigo, pruritus, rash (maculopapular erythematous, or morbilliform), serum sickness-like reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria

Hematologic: Decreased hemoglobin and/or hematocrit, hemolytic anemia, reversible leukopenia; neutropenia, decreased platelets; positive direct and indirect antiglobulin (Coombs') test results; thrombocytopenia

Renal and Genitourinary: Transient increases in blood urea nitrogen (BUN) and serum creatinine concentrations; dysuria, reversible interstitial nephritis; nephrotoxicity, leukorrhea, pruritus vulvae, vaginal discharge, vulvo-vaginitis

Hepatic: Transient increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase concentrations; increased serum bilirubin; transient hepatitis and cholestatic jaundice

Nervous System: Agitation, confusion, diplopia, dizziness, fatigue, headache, hallucinations, insomnia, malaise, paresthesia, somnolence, tremor, toxic paranoid reactions (rarely in patients with renal impairment)

Vertigo, tinnitus, hearing loss and behavioral changes in young children have been reported with cefalexin use.

Other Adverse Effects (AEs): Arthralgia, myalgia, arthritis, joint disorder, back pain, nuchal swelling, cardiac arrhythmia, vasodilatation, dyspnea, superinfection, elevated cholesterol

The following AEs have also been reported for cephalosporin-class antibiotics:

Hypersensitivity reactions including chills, joint pain or inflammation, edema, facial edema, erythema, shock, hypotension, exfoliative dermatitis; anaphylaxis, including a few fatalities, has occurred rarely with cephalosporins; agranulocytosis, aplastic anemia, pancytopenia, thrombocythemia, prolonged prothrombin time, leukocytosis, granulocytosis, monocytosis, lymphocytopenia, basophilia, anemia, epistaxis or hemorrhage; renal dysfunction, toxic nephropathy, genital pruritus, vaginal candidiasis, menstrual irregularities; transient increases in serum γ-glutamyl transferase concentrations; increased serum concentrations of lactate dehydrogenase (LDH); decreased serum albumin and/or total protein; hepatic dysfunction, including cholestasis; epigastric pain, decreased appetite, flatulence, candidiasis, decreased salivation, taste alteration, tenesmus, heartburn; anxiety, nightmares, hyperactivity, nervousness, weakness, hot flushes, alteration in color perception, hypertonia; chest pain, pleural effusion, pulmonary infiltrate, respiratory distress, cough, rhinitis, increased or decreased serum glucose concentration

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced.

OVERDOSE AND TREATMENT

Clinical features of cefalexin overdose may include nausea, vomiting, epigastric distress, diarrhea, and hematuria.
Unless 5 to 10 times the normal cefalexin dose has been ingested, GI decontamination should not be necessary.

It is important to protect the patient's airway and support ventilation and perfusion during overdose. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the GI 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, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for cefalexin overdose; however, it would be extremely unlikely that one of these procedures would be indicated.

There have been reports of hematuria, without renal impairment, in children accidentally ingesting more than 3.5 g of cefalexin in a day. Treatment has been supportive fluids and no sequelae have been reported.

STORAGE CONDITIONS

Store in a dry place at temperatures not exceeding 30°C.
Protect from light.
Keep the products out of sight and reach of children.

AVAILABILITY: Cefalin 250 mg – box of 50 capsules (in flex foil)
Cefalin 500 mg – box of 50 capsules (in flex foil)

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

DATE OF REVISION OF THE PACKAGE INSERT: July 2009

Manufactured by: **ASIAN ANTIBIOTICS, INC.**
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