Cefuroxime Axetil Powder for Oral Suspension: 25 mg/mL & 50 mg/mL in 50 and 100 mL bottles; *Ceftin*® (GlaxoWellcome); (Rx)

Cefuroxime Sodium Powder for Injection: 750 mg, 1.5 g, and 7.5 g (bulk package); *Zinacef*® (GlaxoWellcome); generic; (Rx)

Also available in premixed 750 mg and 1.5 g per 50 mL frozen bags.

CEPHALEXIN

(sef-a-*lex*-in) Keflex®

1st GENERATION CEPHALOSPORIN

Prescriber Highlights

- 1st generation oral cephalosporin (available for injection in other countries)
- May be administered with food (especially if GI upset occurs)
- Most likely adverse effects are GI in nature; hypersensitivity reactions possible
- May need to reduce dose in patients with renal failure

Uses/Indications

There are no approved cephalexin products for veterinary use in the USA. However, it has been used clinically in dogs, cats, horses, rabbits, ferrets, and birds, particularly for susceptible Staphylococcal infections.

Pharmacology/Actions

A first generation cephalosporin, cephalexin exhibits activity against the bacteria usually covered by this class. Cephalosporins are bactericidal against susceptible bacteria and act by inhibiting mucopeptide synthesis in the cell wall resulting in a defective barrier and an osmotically unstable spheroplast. The exact mechanism for this effect has not been definitively determined, but beta-lactam antibiotics have been shown to bind to several enzymes (carboxypeptidases, transpeptidases, endopeptidases) within the bacterial cytoplasmic membrane that are involved with cell wall synthesis. The different affinities that various beta-lactam antibiotics have for these enzymes (also known as penicillin-binding proteins; PBPs) help explain the differences in spectrums of activity of these drugs that are not explained by the influence of beta-lactamases. Like other beta-lactam antibiotics, cephalosporins are generally considered to be more effective against actively growing bacteria.

While there may be differences in MIC's for individual first generation cephalosporins, their spectrums of activity are quite similar. They possess generally excellent coverage against most gram-positive pathogens and variable to poor coverage against most gram-negative pathogens. These drugs are very active *in vitro* against groups *A* beta-hemolytic and B Streptococci, non-enterococcal group D Streptococci (*S. bovis*), *Staphylococcus intermedius* and *aureas*, *Proteus mirabilis* and some strains of *E. coli*, *Klebsiella* spp., Actinobacillus, Pasturella, *Haemophilus equigenitalis*, Shigella and Salmonella. With the exception of *Bacteroides fragilis*, most anaerobes are very susceptible to the first generation agents. Most species of Corynebacteria are susceptible, but *C. equi* (Rhodococcus) is usually resistant. Strains of *Staphylococcus epidermidis* are usually sensitive to the parenterally administered 1st generation drugs, but may have variable susceptibilities to the oral drugs. The following bacteria are regularly resistant to the 1st generation agents: Group D streptococci/enterococci (*S. faecalis, S. faecium*), Methicillin-resistant Staphylococci, *indole-positive Proteus* spp., *Pseudomonas* sp., *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp.

Pharmacokinetics

After oral administration, cephalexin is rapidly and completely absorbed in humans. Cephalexin (base) must be converted to the HCl before absorption can occur and, therefore, absorption can be delayed. There is a form of cephalexin HCl commercially available for oral use that apparently is absorbed more rapidly, but the clinical significance of this is in question. Food apparently has little impact on absorption.

In a study done in dogs and cats (Silley et al. 1988), peak serum levels reached 18.6 micrograms/mL about 1.8 hours after a mean oral dose of 12.7 mg/kg in dogs, and 18.7 micrograms/mL, 2.6 hours after an oral dose of 22.9 mg/kg in cats. Elimination half-lives ranged from 1–2 hours in both species. Bioavailability was about 75% in both species after oral administration.

In horses, oral cephalexin has low bioavailability (approx. 5%) and a short plasma half-life (about 2 hours), but at doses of 30 mg/kg PO q8h sufficient plasma and interstitial levels were achieved to treat gram-positive bacteria (MIC ≤5 mcg/mL) (Davis, Salmon et al. 2005).

In the U.K., an oily suspension of the sodium salt (*Ceporex*® *Injection*—Glaxovet) is apparently available for IM or SC injection in animals. In calves, the sodium salt had a 74% bioavailability after IM injection and a serum half-life of about 90 minutes.

Contraindications/Precautions/Warnings

Cephalosporins are contraindicated in patients with a history of hypersensitivity to them. Because there may be cross-reactivity, use cephalosporins cautiously in patients who are documented hypersensitive to other beta-lactam antibiotics (*e.g.*, penicillins, cefamycins, carbapenems).

Oral systemic antibiotics should not be administered in patients with septicemia, shock or other grave illnesses as absorption of the medication from the GI tract may be significantly delayed or diminished. Parenteral routes (preferably IV) should be used for these cases.

Adverse Effects

Adverse effects with the cephalosporins are usually not serious and have a relatively low frequency of occurrence.

In addition to the adverse effects listed below, cephalexin has reportedly caused salivation, tachypnea and excitability in dogs, and emesis and fever in cats. Nephrotoxicity occurs rarely during therapy with cephalexin, but patients with renal dysfunction, receiving other nephrotoxic drugs or that are geriatric may be more susceptible. Interstitial nephritis, a hypersensitivity reaction, has been reported with many of the cephalosporins including cephalexin. The incidence of these effects is not known.

Hypersensitivity reactions unrelated to dose can occur with these agents and can manifest as rashes, fever, eosinophilia, lymphadenopathy, or full-blown anaphylaxis. The use of cephalosporins in patients documented to be hypersensitive to penicillin-class antibiotics is controversial. In humans, it is estimated 1–15% of patients hypersensitive to penicillins will also be hypersensitive to cephalosporins. The incidence of cross-reactivity in veterinary patients is unknown.

When given orally, cephalosporins may cause GI effects (anorexia, vomiting, diarrhea). Administering the drug with a small meal may help alleviate these effects. Because the cephalosporins may also alter gut flora, antibiotic-associated diarrhea or proliferation of resistant bacteria in the colon can occur.

Rarely, cephalexin has been implicated in causing toxic epidermal necrolysis in cats.

While cephalosporins (particularly cephalothin) have the potential for causing nephrotoxicity at clinically used doses in patients with normal renal function, risks for the occurrence of this adverse effect appear minimal.

High doses or very prolonged use has been associated with neurotoxicity, neutropenia, agranulocytosis, thrombocytopenia, hepatitis, positive Coomb's test, interstitial nephritis, and tubular necrosis. Except for tubular necrosis and neurotoxicity, these effects have an immunologic component.

Reproductive/Nursing Safety

Cephalosporins have been shown to cross the placenta and safe use of them during pregnancy has not been firmly established, but neither have there been any documented teratogenic problems associated with these drugs. However, use only when the potential benefits outweigh the risks. In humans, the FDA categorizes cephalexin as category ***B*** for use during pregnancy (*Animal studies have not yet demonstrated risk to the fetus, but there are no adequate studies in pregnant women; or animal studies have shown an adverse effect, but adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.*)

Small amounts of cephalexin may be distributed into maternal milk; it could potentially affect gut flora in neonates.

Overdosage/Acute Toxicity

Acute oral cephalosporin overdoses are unlikely to cause significant problems other than GI distress, but other effects are possible (see Adverse Effects section).

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving cephalexin and may be of significance in veterinary patients:

- **PROBENECID**: Competitively blocks the tubular secretion of most cephalosporins thereby increasing serum levels and serum half-lives

Laboratory Considerations

- Except for cefotaxime, cephalosporins may cause false-positive **urine glucose determinations** when using cupric sulfate solution (Benedict's Solution, *Clinitest*®). Tests utilizing glucose oxidase (*Tes-Tape*®, *Clinistix*®) are not affected by cephalosporins.
- When using the Jaffe reaction to measure **serum or urine creatinine**, cephalosporins (not ceftazidime or cefotaxime) in high dosages may falsely cause elevated values.
- In humans, particularly with azotemia, cephalosporins have caused a false-positive direct **Coombs' test**. Cephalosporins may also cause falsely elevated **17-ketosteroid** values in urine.

Doses

- **DOGS:**

  For susceptible infections:

  a) For susceptible Staph infections: 30 mg/kg PO q12h (may not be adequate dose for non-UTI's caused by *E. coli*) (Campbell and Rosin 1998)

  b) For pyoderma: 22–35 mg/kg PO q12h or 22 mg/kg PO q8h
  For respiratory infections: 20–40 mg/kg PO q8h; For soft tissue infections: 30–50 mg/kg PO q12h
  For systemic infections: 25–60 mg/kg PO q8h
  For orthopedic infections: 22–30 mg/kg PO q6–8h for 28 days
  For above doses, guideline for duration of therapy is treat for 5–7 days beyond resolution of clinical disease or preferably negative culture (Greene and Watson 1998)

  c) For Gram-positive infections: 22 mg/kg PO twice daily
  For Gram-negative infections: 30 mg/kg PO three times daily (Aucoin 2000)

  d) For treating infectious otitis: 22 mg/kg PO q12h (Kwochka 2002)

  e) For pyometra/metritis: 10–30 mg/kg PO q8–12h (Freshman 2002a)

  f) For UTI: 30–40 mg/kg PO q8h. For acute urethrocystitis, treatment may be 7–10 days for chronic urethrocystitis, up to 4 weeks of treatment may be necessary; for pyelonephritis, 4–8 weeks may be adequate (Brovida 2003)

  g) For neonates: 10–30 mg/kg PO (weak neonates should be given via stomach tube) twice daily–three times daily (Freshman 2002b)

  h) For juvenile cellulitis in 3–16 week old puppies: 20 mg/kg PO three times daily (Macintire 2004)

  i) For recurrent pyoderma: 22 mg/kg PO q12h (use at q8h for deep pyoderma) (Hillier 2006b)

  j) For superficial and deep pyoderma: 22–33 mg/kg PO two to three times daily (Beale and Murphy 2006)

- **CATS:**

  For susceptible infections:

  a) For soft tissue infections: 30–50 mg/kg PO q12h
  For systemic infections: 35 mg/kg PO q6–8h.
  For above doses, guideline for duration of therapy is treat for 5–7 days beyond resolution of clinical disease or preferably negative culture (Greene and Watson 1998)

  b) 22 mg/kg PO q8h; administer with food if GI upset occurs (Vaden and Papich 1995)

  c) For Gram+ infections: 22 mg/kg PO twice daily

  d) For Gram- infections: 30 mg/kg PO three times daily (Aucoin 2000)

  e) 20–40 mg/kg PO q8h (Lappin 2002a)

- **RABBITS/RODENTS/SMALL MAMMALS:**

  a) Rabbits: 11–22 mg/kg PO q8h (Ivey and Morrisey 2000)

  b) Guinea pigs: 50 mg/kg IM q24h (Adamcak and Otten 2000)

- **FERRETS:**

  For susceptible infections:

  a) 15–25 mg/kg PO 2–3 times daily (Williams 2000)

- **HORSES:**

  For susceptible infections:

  a) 30 mg/kg PO q8h (Davis, Salmon et al. 2005)

  b) 22–33 mg/kg PO q6h (Brumbaugh 1987)

- **BIRDS:**

  For susceptible infections:

  a) 35–50 mg/kg PO four times daily (using suspension); most preps are well accepted (Clubb 1986)

  b) 40–100 mg/kg q6h PO (Hoeffer 1995)

  c) Ratites: 15–22 mg/kg PO three times daily; For megabacteriosis: 50 mg/kg PO 4 times daily for 5 days (Jenson 1998)

Monitoring
- Because cephalosporins usually have minimal toxicity associated with their use, monitoring for efficacy is usually all that is required
- Patients with diminished renal function may require intensified renal monitoring. Serum levels and therapeutic drug monitoring are not routinely done with these agents

Chemistry/Synonyms
A semi-synthetic oral cephalosporin, cephalexin (as the monohydrate) occurs as a white to off-white crystalline powder. It is slightly soluble in water and practically insoluble in alcohol.

Cephalexin may also be known as: cefalexin, 66873, or cefalexinum; many trade names are available.

Storage/Stability
Cephalexin tablets, capsules, and powder for oral suspension should be stored at room temperature (15–30°C) in tight containers. After reconstitution, the oral suspension is stable for 2 weeks.

Dosage Forms/Regulatory Status
VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Cephalexin Capsules: 250 mg, 333 mg, 500 mg & 750 mg; Tablets: 250 mg & 500 mg; *Keflex*® (Advancis); generic; (Rx)

Cephalexin Powder for Oral Suspension: 125 mg/5mL and 250 mg/5 mL (after reconstitution) in 100 mL and 200 mL; *Keflex*® (Advancis); generic; (Rx)

CEPHAPIRIN SODIUM
CEPHAPIRIN BENZATHINE

(sef-a-*pye*-rin) Cefa-Lak®, Cefa-Dri®

1st GENERATION CEPHALOSPORIN

Prescriber Highlights
- 1st generation intramammary cephalosporin
- Potentially could cause hypersensitivity reactions
- Watch withdrawal times

Uses/Indications
In the USA, there are no longer parenterally administered cephapirin products available.

An intramammary cephapirin sodium product (*Cefa-Lak*®, *ToDAY*®—Fort Dodge) is approved for use in the treatment of mastitis in lactating dairy cows and cephapirin benzathine (*Cefa-Dri*®, *ToMORROW*®—Fort Dodge) is approved in dry cows.

Pharmacology/Actions
A first generation cephalosporin, cephapirin exhibits activity against the bacteria usually covered by this class. A cephalothin disk is usually used to determine bacterial susceptibility to this antibiotic when using the Kirby-Bauer method. Cephalosporins are usually bactericidal against susceptible bacteria and act by inhibiting mucopeptide synthesis in the cell wall resulting in a defective barrier and an osmotically unstable spheroplast. The exact mechanism for this effect has not been definitively determined, but beta-lactam antibiotics have been shown to bind to several enzymes (carboxypeptidases, transpeptidases, endopeptidases) within the bacterial cytoplasmic membrane that are involved with cell wall synthesis. The different affinities that various beta-lactam antibiotics have for these enzymes (also known as penicillin-binding proteins; PBPs) help explain the differences in these drugs' spectrums of activity that are not explained by the influence of beta-lactamases. Like other beta-lactam antibiotics, cephalosporins are generally considered more effective against actively growing bacteria.

Pharmacokinetics
In cattle when used systemically, the apparent volume of distribution has been reported as 0.335–0.399 L/kg; total body clearance is 12.66 mL/min/kg and serum elimination half-life is about 64–70 minutes in cattle.

Contraindications/Precautions/Warnings
Cephalosporins are contraindicated in patients with a history of hypersensitivity to them. Because there may be cross-reactivity, use cephalosporins cautiously in patients who are documented hypersensitive to other beta-lactam antibiotics (*e.g.*, penicillins, cefamycins, carbapenems).

Adverse Effects
Adverse effects with the cephalosporins are usually not serious and have a relatively low frequency of occurrence.

Potentially, hypersensitivity reactions could occur with intramammary infusion. Hypersensitivity reactions unrelated to dose can occur with these agents and can manifest as rashes, fever, eosinophilia, lymphadenopathy, or full-blown anaphylaxis. The use of cephalosporins in patients documented to be hypersensitive to penicillin-class antibiotics is controversial. In humans, it is estimated 1–15% of patients hypersensitive to penicillins will also be hypersensitive to cephalosporins. The incidence of cross-reactivity in veterinary patients is unknown.

Reproductive/Nursing Safety
Cephalosporins have been shown to cross the placenta and safe use of them during pregnancy has not been firmly established, but neither have there been any documented teratogenic problems associated with these drugs. See label information for more information.

Overdosage/Acute Toxicity
No clinical effects would be expected but if used at doses or rates higher than labeled, withdrawal times may be prolonged.

Drug Interactions
No significant concerns when used via the intramammary route

Laboratory Considerations
No significant concerns when used via the intramammary route

Doses
- **CATTLE:**

For mastitis:

a) Lactating cow (*Cefa-Lak*®): After milking out udder, clean and dry teat area. Swab teat tip with alcohol wipe and allow to dry. Insert tip of syringe into teat canal; push plunger to instill entire contents. Massage quarter and do not milk out for 12 hours. May repeat dose q12h. (Label directions; *Cefa-Lak*®—Fort Dodge)

b) Dry Cow (*Cefa-Dri*®): Same basic directions as above, but should be done at the time of drying off and not later than 30 days prior to calving. (Label directions; *Cefa-Dri*®—Fort Dodge)