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 **Combs' test**
- Cephalosporins may also cause falsely elevated **17-ketosteroid** values in urine

Doses -

- **DOGS:**

For susceptible infections:

a) 22 mg/kg PO twice daily. Treat skin and soft tissue infections for at least 3 days, and GU infections for at least 7 days. Treat for at least 48 hours after animal is afebrile and asymptomatic. Reevaluate therapy if no response after 3 days of treatment. Maximum therapy is 30 days. (Package Insert; *Cefa-Tabs*®—Fort-Dodge).

b) 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)

c) For UTI: 11–22 mg/kg PO q12h for 7–30 days
For skin, pyoderma: 22–35 mg/kg PO q12h for 3–30 days
For systemic, orthopedic infections: 22 mg/kg PO q8–12h for 30 days (Greene and Watson 1998)

d) 10 mg/kg q12h for susceptible Gram+ infections; 30 mg/kg q8h for susceptible Gram- infections (Aucoin 2000)

e) For canine pyoderma/infectious otitis: 22 mg/kg PO q12h (Kwochka 2003c); (Kwochka 2002)

f) For UTI: 10–20 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 superficial and deep bacterial pyoderma: 22–33 mg/kg PO 2-3 times daily (Beale and Murphy 2006)

- **CATS:**

For susceptible infections:

a) For UTI: 22 mg/kg PO once daily for 21 days or less
For skin, pyoderma: 22–35 mg/kg PO q12h for 3–30 days
For systemic, orthopedic infections: 22 mg/kg PO q8–12h for 30 days (Greene and Watson 1998)

b) 10 mg/kg q12h for susceptible gram-positive infections; 30 mg/kg q8h for susceptible gram-negative infections (Aucoin 2000)

c) 22 mg/kg PO q12h (Lappin 2002a)

- **FERRETS:**

For susceptible infections:

a) 15–20 mg/kg PO twice daily (Williams 2000)

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 performed with these agents.

Chemistry/Synonyms

A semisynthetic cephalosporin antibiotic, cefadroxil occurs as a white to yellowish-white, crystalline powder that is soluble in water and slightly soluble in alcohol. The commercially available product is available as the monohydrate.

Cefadroxil may also be known as: BL-S578; cefadroxilum, cephadroxil, or MJF-11567-3; many trade names are available.

Storage/Stability/Compatibility

Cefadroxil 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 14 days when kept refrigerated (2–8°C).

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Cefadroxil Powder for Oral Suspension: 50 mg/mL in 15 mL and 50 mL btls (orange-pineapple flavor); *Cefa-Drops*® (Fort-Dodge) (Rx). Approved for use in dogs and cats.

HUMAN-LABELED PRODUCTS:

Cefadroxil Oral Tablets: 1 gram; *Duricef*® (Bristol-Myers Squibb); generic; (Rx)

Cefadroxil Oral Capsules: 500 mg; *Duricef*® (Bristol-Myers Squibb); generic; (Rx)

Cefadroxil Powder for Oral Suspension: 125 mg/5 mL, 250 mg/5 mL, & 500 mg/5 mL in 50 mL, 75 mL and 100 mL; *Duricef*® (Bristol-Myers Squibb); (Rx)

CEFAZOLIN SODIUM

(sef-*a*-zoe-lin) Ancef®, Kefzol®, Zolicef®

1st GENERATION CEPHALOSPORIN

Prescriber Highlights

- **1st generation parenteral cephalosporin**
- **Potentially could cause hypersensitivity reactions**
- **Can cause pain on IM injection; Give IV over 3–5 minutes (or more)**
- **May need to reduce dose in renal failure**

Uses/Indications

In the United States, there are no cefazolin products approved for veterinary species but it has been used clinically in several species when an injectable, first generation cephalosporin is indicated. It is used for surgical prophylaxis, and for variety of systemic infections (including orthopedic, soft tissue, sepsis) caused by susceptible bacteria. Most commonly given every 6–8 hours via parenteral routes, cefazolin constant rate intravenous infusion protocols are being developed as cefazolin is a time (above MIC)-dependent antibiotic, and serum/tissue concentrations can remain above MIC.

Pharmacology/Actions

A first generation cephalosporin, cefazolin exhibits activity against the bacteria usually covered by this class. First generation cephalosporins are usually bactericidal and act via inhibition of cell wall synthesis.

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; 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* spp., *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp.

Pharmacokinetics

Cefazolin is not appreciably absorbed after oral administration and must be given parenterally to achieve therapeutic serum levels. Absorbed drug is excreted unchanged by the kidneys into the urine. Elimination half-lives may be significantly prolonged in patients with severely diminished renal function.

In dogs, peak levels occur in about 30 minutes after IM administration. The apparent volume of distribution at steady state is 700 mL/kg, total body clearance of 10.4 mL/min/kg with a serum elimination half-life of 48 minutes. Approximately 64% of the clearance can be attributed to renal tubular secretion. The drug is approximately 16–28% bound to plasma proteins in dogs.

In horses, the apparent volume of distribution at steady state is 190 mL/kg, total body clearance of 5.51 mL/min/kg with a serum elimination half-life of 38 minutes when given IV and 84 minutes after IM injection (gluteal muscles). Cefazolin is about 4–8% bound to equine plasma proteins. Because of the significant tubular secretion of the drug, it would be expected that probenecid administration would alter the kinetics of cefazolin. One study performed in horses (Donecker, Sams, and Ashcroft 1986), did not show any effect, but the authors concluded that the dosage of probenecid may have been sub-therapeutic in this species.

In calves, the volume of distribution is 165 mL/kg, and had a terminal elimination half-life of 49–99 minutes after IM administration.

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).

Patients in renal failure may need dosage adjustments.

Adverse Effects

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

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.

Cephalosporins can cause pain at the injection site when administered intramuscularly, although this effect occurs less with cefazolin than with other agents. Sterile abscesses or other severe local tissue reactions are possible but are much less common. Thrombophlebitis is also possible after IV administration of these drugs.

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 Comb's test, interstitial nephritis, and tubular necrosis. Except for tubular necrosis and neurotoxicity, these effects have an immunologic component. Cefazolin may be more likely than other cephalosporins to cause seizures at very high doses.

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 this drug 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.*)

Cefazolin is distributed into milk and could potentially alter neonatal gut flora. Use with caution in nursing dams.

Overdosage/Acute Toxicity

Cephalosporin overdoses are unlikely to cause significant problems, but other effects are possible (see Adverse Effects section). Very high doses given IV rapidly could potentially cause seizures.

Drug Interactions

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

- **NEPHROTOXIC DRUGS**: The concurrent use of parenteral aminoglycosides or other nephrotoxic drugs (*e.g.*, amphotericin B) with cephalosporins is somewhat controversial. Potentially, cephalosporins could cause additive nephrotoxicity when used with these drugs, but this interaction has only been well documented with cephaloridine (no longer marketed). Nevertheless, use caution.
- **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

Note: If injecting IM, must be injected into a large muscle mass. IV injections should not be given faster than over 3–5 minutes.

DOGS:

For susceptible infections:

a) For surgical prophylaxis: Orthopedic procedures: 20 mg/kg IV at induction followed by 20 mg/kg IV every 90 minutes until wound closure; Soft tissue surgery: 20 mg/kg IV at time of surgery followed by a second dose of 20 mg/kg SC 6 hours later (Trepanier 2003)

b) Gram+ infections: 10 mg/kg IV, or IM q8h; 10–30 mg/kg IV q8h

Gram- infections: 30 mg/kg IM or SC; 10–30 mg/kg IV q8h (Aucoin 2000)

c) For sepsis: 20–25 mg/kg IV q4–8h (Hardie 2000)

d) For surgical prophylaxis: 8 mg/kg IV just before and during surgery 1 hour apart or 20–22 mg/kg IV just before and during surgery 2 hours apart.

For systemic infections: 5–25 mg/kg IM or IV q6–8h as long as necessary.

For orthopedic infections: 22 mg/kg IV, IM or SC q6–8h for 7 days or less.

For sepsis, bacteremia: 15–25 mg/kg IV, IM or SC q4–8h for 7 days or less (Greene and Watson 1998)

e) For infections in neonates: 10–30 mg/kg IV or IO (intraosseous) q8h (Kampschmidt 2006)

CATS:

For susceptible infections:

a) Gram+ infections: 10 mg/kg IV, or IM q8h; 10–30 mg/kg IV q8h

Gram- infections: 30 mg/kg IM or SC; 10–30 mg/kg IV q8h (Aucoin 2000)

b) For surgical prophylaxis: Orthopedic procedures: 20 mg/kg IV at induction followed by 20 mg/kg IV every 90 minutes until wound closure; Soft tissue surgery: 20 mg/kg IV at time of surgery followed by a second dose of 20 mg/kg SC 6 hours later (Trepanier 2003)

c) For sepsis: 20–25 mg/kg IV q4–8h (Hardie 2000)

d) For systemic infections: 33 mg/kg IV, or IM q8–12h as long as necessary (Greene and Watson 1998)

e) 20–25 mg/kg q8h IM or IV (Lappin 2002a)

f) For infections in neonates: 10–30 mg/kg IV or IO (intraosseous) q8h (Kampschmidt 2006)

HORSES:

For susceptible infections:

a) 25 mg/kg IV, IM q6h (Bertone 2003b)

b) 25 mg/kg IV, IM q6–8h (Papich 2003a)

c) Foals: 20 mg/kg IV q8–12h (Caprile and Short 1987); (Brumbaugh 1999)

d) Neonatal foals: 15–20 mg/kg IV q8h (Magdesian 2003)

REPTILES:

For susceptible infections:

a) Chelonians: 22 mg/kg IM q24h (Johnson 2002)

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

An injectable, semi-synthetic cephalosporin antibiotic, cefazolin sodium occurs as a practically odorless or having a faint odor, white to off-white, crystalline powder or lyophilized solid. It is freely soluble in water and very slightly soluble in alcohol. Each gram of the injection contains 2 mEq of sodium. After reconstitution, the solution for injection has a pH of 4.5–6 and has a light-yellow to yellow color.

Cefazolin sodium may also be known as: 46083, cefazolinum natricum, cephazolin sodium, or SKF-41558; many trade names are available.

Storage/Stability/Compatibility

Cefazolin sodium powder for injection and solutions for injection should be protected from light. The powder for injection should be stored at room temperature (15–30°C); avoid temperatures above 40°C. The frozen solution for injection should be stored at temperatures no higher than -20°C.

After reconstitution, the solution is stable for 24 hours when kept at room temperature; 96 hours if refrigerated. If after reconstitution, the solution is immediately frozen in the original container, the preparation is stable for at least 12 weeks when stored at -20°C.

The following drugs or solutions are reportedly **compatible** with cephapirin: Amino acids 4.25%/dextrose 25%, D_5W in Ringer's, D_5W in Lactated Ringer's, D_5W in sodium chloride 0.2%–0.9%, D_5W, $D_{10}W$, Ringer's Injection, Lactated Ringer's Injection, normal saline, metronidazole, verapamil HCl and vitamin B-complex.

The following drugs or solutions are reportedly **incompatible** or only compatible in specific situations with cefazolin: amikacin sulfate, amobarbital sodium, ascorbic acid injection, bleomycin sulfate, calcium chloride/gluconate, cimetidine HCl, erythromycin gluceptate, kanamycin sulfate, lidocaine HCl, oxytetracycline HCl, pentobarbital sodium, polymyxin B sulfate, tetracycline HCl and vitamin B-complex with C injection.

Compatibility is dependent upon factors such as pH, concentration, temperature and diluent used; consult specialized references or a hospital pharmacist for more specific information.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Cefazolin Sodium Powder for Injection: 500 mg, 1g, 5g, 10g, and 20g; generic (Apothecon); (Rx)

Cefazolin Sodium for Injection (IV infusion): 500 mg, 1 g; in 50 mL plastic containers, or duplex bags, *Ancef*® (SKB); generic; (Rx)

CEFEPIME HCL

(sef-eh-***pim***) Maxipime®

4th GENERATION CEPHALOSPORIN

Prescriber Highlights

- Injectable 4th generation cephalosporin that is more active against some gram-negative & gram-positive bacteria than 3rd generation cephalosporins
- Potentially useful for treating neonatal foals & dogs with serious infections
- Limited clinical experience in veterinary medicine
- Adverse effects most likely seen in small animals or foals would be GI-related (diarrhea)
- Treatment may be very expensive

Uses/Indications

Cefepime is a semi-synthetic 4th generation cephalosporin with enhanced activity against many gram-negative and gram-positive pathogens. It potentially may be useful in treating serious infections in dogs or foals particularly when aminoglycosides, fluoroquinolones or other more commonly used beta-lactam drugs are ineffective or contraindicated.

Pharmacology/Actions

Cefepime, like other cephalosporins, is usually bactericidal and acts by inhibiting cell wall synthesis. It is classified as a 4th-generation cephalosporin, implying increased gram-negative activity (particularly against *Pseudomonas*) and better activity against many gram-positive bacteria than would be seen with the 3rd generation agents. It rapidly penetrates into gram-negative bacteria and targets penicillin-binding proteins (PBPs). Cefepime does not readily induce beta-lactamases and is highly resistant to hydrolysis by them.

Cefepime has activity against many gram-positive aerobes including many species and strains of Staphylococci and Streptococci. It is not clinically effective in treating infections caused by enterococci, *L. monocytogenes,* or methicillin-resistant staphylococci.

Cefepime has good activity against many gram-negative bacteria and has better activity than other cephalosporins against many Enterobacteriaceae including *Enterobacter* spp., *E. coli*, *Proteus* spp. and Klebsiella. Its activity against *Pseudomonas* is similar to, or slightly less than, that of ceftazidime.

Cefepime also has activity against certain atypicals like *Mycobacterium avium-intracellulare* complex.

Some anaerobes are sensitive to cefepime, but *Clostridia* and *Bacteroides* are not.

For more information on cephalosporin pharmacology and spectrums of activity, refer to the Cephalosporin monograph.

Pharmacokinetics

Cefepime is not absorbed from the GI tract and must be administered parenterally. In dogs, cefepime's volume of distribution at steady state is approximately 0.14 L/kg, elimination half-life about 1.1 hours and clearance 0.13 L/kg/hr.

In neonatal foals, cefepime's volume of distribution at steady state is approximately 0.18 L/kg, elimination half-life about 1.65 hours and clearance 0.08 L/kg/hr.

In humans, volume of distribution is about 18 L in adults; 20% of the drug is bound to plasma proteins. Elimination half-life is about 2 hours. Approximately 85% of a dose is excreted unchanged into the urine, less than 1% is metabolized.

Contraindications/Precautions/Warnings

No specific information is available for veterinary patients. Cefepime is contraindicated in human patients hypersensitive to it or other cephalosporins. Dosage adjustment is recommended in humans with severe renal impairment.

Adverse Effects

As usage of cefepime in animals has been very limited, a comprehensive adverse effect profile has not been determined.

There are some reports of dogs or foals developing loose stools or diarrhea after receiving cefepime. IM injections may be painful (alleviated by using 1% lidocaine as diluent).

Human patients generally tolerate cefepime well. Injection site inflammation and rashes occur in approximately 1% of treated patients. Gastrointestinal effects (dyspepsia, diarrhea) occur in less than 1% treated patients. Hypersensitivity reactions including anaphylaxis are possible. Rarely, patients with renal dysfunction who have received cefepime without any dosage adjustment will develop neurologic effects (see Overdosage).

Reproductive/Nursing Safety

Studies performed in pregnant mice, rats, and rabbits demonstrated no overt fetal harm. In humans, the FDA categorizes cefepime 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.*)

Cefepime enters maternal milk in very low concentrations. Although probably safe for nursing offspring, the potential for adverse effects cannot be ruled out, particularly alterations to gut flora with resultant diarrhea.

Overdosage/Acute Toxicity

No specific information was located for acute toxicity in veterinary patients.

Humans with impaired renal function receiving inadvertent overdoses have developed encephalopathy, seizures and neuromuscular excitability.

Drug Interactions

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

- **AMINOGLYCOSIDES**: Potential for increased risk of nephrotoxicity—monitor renal function

Laboratory Considerations

- Cefepime may cause false-positive **urine glucose determinations** when using the copper reduction method (Benedict's solution, Fehling's solution, *Clinitest*®); tests utilizing glucose oxidase (*TesTape*®, *Clinistix*®) are not affected by cephalosporins
- In humans, particularly with azotemia, cephalosporins have caused a false-positive direct **Coombs' test**

Doses

- **DOGS:**

For susceptible infections:

a) 40 mg/kg IV q6h (Gardner and Papich 2001)