- **FOOD, ANTACIDS:** The amount of penicillamine absorbed from the GI tract may be reduced by the concurrent administration of food or antacids
- **GOLD COMPOUNDS:** May increase the risk of hematologic and/or renal adverse reactions
- **IMMUNOSUPPRESSANT DRUGS** (*e.g.*, **cyclophosphamide**, **azathioprine**, but **not corticosteroids**): May increase the risk of hematologic and/or renal adverse reactions
- **PHENYLBUTAZONE:** May increase the risk of hematologic and/or renal adverse reactions

Laboratory Considerations

- When using **technetium Tc 99m gluceptate** to visualize the kidneys, penicillamine may chelate this agent and form a compound that is excreted via the hepatobiliary system resulting in gallbladder visualization that could confuse the results.

Doses

- **DOGS:**

For copper-associated hepatopathy:

a) 10–15 mg/kg PO q12h on an empty stomach. Do not give concurrently with any medication, including zinc or a vitamin-mineral supplement. (Jergens and Willard 2000)

b) 10–15 mg/kg PO two times a day. If vomiting ensues the dose is split and given at mealtime or with a small portion of meat. (Center 2002)

c) 10–15 mg/kg PO two times a day 30 minutes prior to food. Start low and increase. (Webb 2007b)

For cystine urolithiasis:

a) 15 mg/kg: PO twice daily. If nausea and vomiting occur, mix with food or give at mealtime. Some dogs may need to have the dosage slowly increased to full dose in order to tolerate the drug. (Osborne, Hoppe, and O'Brien 1989)

b) 15 mg/kg: PO twice daily with food (Lage, Polzin, and Zenoble 1988)

For lead poisoning:

a) After initial therapy regimen with CaEDTA and if continued therapy is desired at home, may give penicillamine at 110 mg/kg/day, PO divided q6–8h for 1–2 weeks. If vomiting, depression, and anorexia occur, may reduce dose to 33–55 mg/kg/day divided q6–8h, which should be better tolerated. (Mount 1989)

b) As an alternate or adjunct to CaEDTA: 110 mg/kg/day divided q6–8h PO 30 minutes before feeding for 1–2 weeks. If vomiting a problem may premedicate with dimenhydrinate (2–4 mg/kg PO). Alternatively, may give 33–55 mg/kg/day divided as above. Dissolving medication in juice may facilitate administration. (Nicholson 2000)

- **CATS:**

For lead poisoning:

a) After initial therapy with CaEDTA and if blood lead is greater than 0.2 ppm at 3–4 weeks post-treatment, may repeat CaEDTA or give penicillamine at 125 mg q12h PO for 5 days. (Reid and Oehme 1989)

- **SMALL RUMINANTS:**

Note: When used in food animals, FARAD recommends a minimum milk withdrawal time of 3 days after the last treatment and a 21-day preslaughter withdrawal. (Haskell, Payne et al. 2005)

For copper toxicity:

a) 52 mg/kg daily for 6 days is sometimes successful (Reilly 2004)

- **BIRDS:**

For adjunctive treatment of lead poisoning:

a) 55 mg/kg PO q12h for 1–2 weeks. It has been suggested that combining CaEDTA and penicillamine for several days until symptoms dissipate followed by a 3–6 week treatment with penicillamine as the best regimen for lead toxicity. (Jones 2007a)

Monitoring

- Monitoring of penicillamine therapy is dependent upon the reason for its use; refer to the references in the Dose section above for further discussion on the diseases and associated monitoring of therapy.

Client Information

- This drug should preferably be given on an empty stomach, at least 30 minutes before feeding. If the animal develops problems with vomiting or anorexia, three remedies have been suggested:
  1) Give the same total daily dose, but divide into smaller individual doses and give more frequently
  2) Temporarily reduce the daily dose and gradually increase to recommended dosage, or
  3) Give with meals (will probably reduce amount of drug absorbed).

Chemistry/Synonyms

A monothiol chelating agent that is a degradation product of penicillins, penicillamine occurs as a white or practically white, crystalline powder with a characteristic odor. Penicillamine is freely soluble in water and slightly soluble in alcohol with pK_a values of 1.83, 8.03, and 10.83.

Penicillamine may also be known as: D-Penicillamine, beta,beta-Dimethylcysteine, D-3-Mercaptovaline, penicillaminum, *Depen*® and *Cuprimine*®.

Storage/Stability

Penicillamine should be stored at room temperature (15–30°C). The capsules should be stored in tight containers; tablets in well-closed containers.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Penicillamine Titratable Tablets: 250 mg (scored); *Depen*® (Wallace); (Rx)

Penicillamine Capsules: 125 mg & 250 mg; *Cuprimine*® (Merck); (Rx)

PENICILLINS, GENERAL INFORMATION

(pen-i-***sill***-in)

Uses/Indications

Penicillins have been used for a wide range of infections in various species. FDA-approved indications/species, as well as non-approved uses, are listed in the Uses/Indications and Dosage section for each drug.

Pharmacology/Actions

Penicillins 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 spectrums of activity the drugs have that are not explained by the influence of beta-lactamases. Like other beta-lactam antibiotics, penicillins are generally considered more effective against actively growing bacteria.

The clinically available penicillins encompass several distinct classes of compounds with varying spectrums of activity: The so-called natural penicillins including penicillin G and V; the penicillinase-resistant penicillins including cloxacillin, dicloxacillin, oxacillin, nafcillin, and methicillin; the aminopenicillins including ampicillin, amoxicillin, cyclacillin, hetacillin, and bacampicillin; extended-spectrum penicillins including carbenicillin, ticarcillin, piperacillin, azlocillin, and mezlocillin; and the potentiated penicillins including amoxicillin-potassium clavulanate, ampicillin-sulbactam, piperacillin-tazobactam, and ticarcillin-potassium clavulanate.

The natural penicillins (G and K) have similar spectrums of activity, but penicillin G is slightly more active *in vitro* on a weight basis against many organisms. This class of penicillin has *in vitro* activity against most spirochetes and gram-positive and gram-negative aerobic cocci, but not penicillinase-producing strains. They have activity against some aerobic and anaerobic gram-positive bacilli such as *Bacillus anthracis*, *Clostridium* spp. (not *C. difficile*), Fusobacterium, and Actinomyces. The natural penicillins are customarily inactive against most gram-negative aerobic and anaerobic bacilli, and all Rickettsia, mycobacteria, fungi, Mycoplasma, and viruses.

The penicillinase-resistant penicillins have a narrower spectrum of activity than the natural penicillins. Their antimicrobial efficacy is aimed directly against penicillinase-producing strains of gram-positive cocci, particularly staphylococcal species; these drugs are sometimes called anti-staphylococcal penicillins. There are documented strains of Staphylococcus that are resistant to these drugs (so-called methicillin-resistant or oxacillin-resistant Staph), but these strains have only begun to be a significant problem in veterinary species. While this class of penicillins does have activity against some other gram-positive and gram-negative aerobes and anaerobes, other antibiotics are usually better choices. The penicillinase-resistant penicillins are inactive against Rickettsia, mycobacteria, fungi, Mycoplasma, and viruses.

The aminopenicillins, also called the "broad-spectrum" or ampicillin penicillins, have increased activity against many strains of gram-negative aerobes not covered by either the natural penicillins or penicillinase-resistant penicillins, including some strains of *E. coli*, Klebsiella, and Haemophilus. Like the natural penicillins, they are susceptible to inactivation by beta-lactamase-producing bacteria (*e.g.,* Staph aureus). Although not as active as the natural penicillins, they do have activity against many anaerobic bacteria, including Clostridial organisms. Organisms that are generally not susceptible include *Pseudomonas aeruginosa*, Serratia, Indole-positive Proteus (*Proteus mirabilis* is susceptible), Enterobacter, Citrobacter, and Acinetobacter. The aminopenicillins also are inactive against Rickettsia, mycobacteria, fungi, Mycoplasma, and viruses.

The extended-spectrum penicillins, sometimes called anti-pseudomonal penicillins, include both alpha-carboxypenicillins (carbenicillin and ticarcillin) and acylaminopenicillins (piperacillin, azlocillin, and mezlocillin). These agents have similar spectrums of activity as the aminopenicillins but with additional activity against several gram-negative organisms of the family Enterobacteriaceae, including many strains of *Pseudomonas aeruginosa*. Like the aminopenicillins, these agents are susceptible to inactivation by beta-lactamases.

In order to reduce the inactivation of penicillins by beta-lactamases, potassium clavulanate and sulbactam have been developed to inactivate these enzymes and extend the spectrum of those penicillins. When used with penicillin, these combinations are often effective against many beta-lactamase-producing strains of otherwise resistant *E. coli*, *Pasturella* spp., *Staphylococcus* spp., Klebsiella, and Proteus. Type I beta-lactamases are often associated with *E. coli*, Enterobacter, and Pseudomonas, and not generally inhibited by clavulanic acid.

Pharmacokinetics (General)

The oral absorption characteristics of the penicillins are dependent upon its class. Penicillin G is the only available oral penicillin that is substantially affected by gastric pH and can be completely inactivated at a pH of less than 2. The other orally available penicillins are resistant to acid degradation but bioavailability can be decreased (not amoxicillin) by the presence of food. Of the orally administered penicillins, penicillin V and amoxicillin tend to have the greatest bioavailability in their respective classes.

Penicillins are generally distributed widely throughout the body. Most drugs attain therapeutic levels in the kidneys, liver, heart, skin, lungs, intestines, bile, bone, prostate, and peritoneal, pleural, and synovial fluids. Penetration into the CSF and eye only occur with inflammation and may not reach therapeutic levels. Penicillins are bound in varying degrees to plasma proteins and cross the placenta.

Most penicillin's are rapidly excreted largely unchanged by the kidneys into the urine via glomerular filtration and tubular secretion. Probenecid can prolong half-lives and increase serum levels by blocking the tubular secretion of penicillins. Except for nafcillin and oxacillin, hepatic inactivation and biliary secretion is a minor route of excretion.

Contraindications/Precautions/Warnings

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

Do not administer systemic antibiotics orally 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 (preferably IV) routes should be used for these cases. Certain species (snakes, birds, turtles, Guinea pigs, and chinchillas) are reportedly sensitive to procaine penicillin G.

High doses of penicillin G sodium or potassium, particularly in small animals with a preexisting electrolyte abnormality, renal disease, or congestive heart failure may cause electrolyte imbalances. Other injectable penicillins, such as ticarcillin, carbenicillin, and ampicillin, have significant quantities of sodium per gram and may cause electrolyte imbalances when used in large dosages in susceptible patients.

Adverse Effects

Adverse effects with the penicillins 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, neu-

tropenia, agranulocytosis, thrombocytopenia, leukopenia, anemias, lymphadenopathy, or full-blown anaphylaxis. In humans, it is estimated that up to 15% of patients hypersensitive to cephalosporins will also be hypersensitive to penicillins. The incidence of cross-reactivity in veterinary patients is unknown.

When given orally, penicillins may cause GI effects (anorexia, vomiting, diarrhea). Because the penicillins may also alter gut flora, antibiotic-associated diarrhea can occur and allow the proliferation of resistant bacteria in the colon (superinfections).

Neurotoxicity (*e.g.*, ataxia in dogs) has been associated with very high doses or very prolonged use. Although the penicillins are not considered hepatotoxic, elevated liver enzymes have been reported. Other effects reported in dogs include tachypnea, dyspnea, edema, and tachycardia.

Some penicillins (ticarcillin, carbenicillin, azlocillin, mezlocillin, piperacillin and nafcillin) have been implicated in causing bleeding problems in humans. These drugs are infrequently used systemically in veterinary species and veterinary ramifications of this effect are unclear.

Reproductive/Nursing Safety

Penicillins 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. 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.*) However, use only when the potential benefits outweigh the risks.

Penicillins are excreted in maternal milk in low concentrations; use potentially could cause diarrhea, candidiasis, or allergic response in the nursing offspring.

Overdosage/Acute Toxicity

Acute oral penicillin overdoses are unlikely to cause significant problems other than GI distress, but other effects are possible (see Adverse effects). In humans, very high dosages of parenteral penicillins, especially in patients with renal disease, have induced CNS effects.

Drug Interactions

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

- **AMINOGLYCOSIDES**: *In vitro* studies have demonstrated that penicillins can have synergistic or additive activity against certain bacteria when used with aminoglycosides or cephalosporins.
- **BACTERIOSTATIC ANTIBIOTICS** (*e.g.*, **chloramphenicol, erythromycin, tetracyclines**): Use with penicillins is generally not recommended, particularly in acute infections where the organism is proliferating rapidly as penicillins tend to perform better on actively growing bacteria.
- **PROBENECID**: Competitively blocks the tubular secretion of most penicillins, thereby increasing serum levels and serum half-lives.

Laboratory Considerations

- Penicillins 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 penicillin.
- In humans, clavulanic acid and high dosages of piperacillin have caused a false-positive direct **Combs' test**.
- As penicillins and other beta-lactams can inactivate aminoglycosides *in vitro* (and *in vivo* in patients in renal failure), serum concentrations of **aminoglycosides** may be falsely decreased if the patient is also receiving beta-lactam antibiotics and the serum is stored prior to analysis. It is recommended that if the assay is delayed, samples be frozen and, if possible, drawn at times when the beta-lactam antibiotic is at a trough.

Monitoring

- Because penicillins usually have minimal toxicity associated with their use, monitoring for efficacy is usually all that is required unless toxic signs develop.
- Serum levels and therapeutic drug monitoring are not routinely done with these agents.

Client Information

- Owners should be instructed to give oral penicillins on an empty stomach, unless using amoxicillin or GI effects (anorexia, vomiting) occur.
- Compliance with the therapeutic regimen should be stressed.
- Reconstituted oral suspensions should be kept refrigerated and discarded after 14 days, unless labeled otherwise.

PENICILLIN G

(pen-i-*sill*-in *jee*)

PENICILLIN ANTIBIOTIC

Prescriber Highlights

- **Prototypical penicillin agent used for susceptible gram-positive aerobes & anaerobes; best used parenterally**
- **Contraindications: Known hypersensitivity (unless no other options)**
- **Adverse Effects: Hypersensitivity possible. Very high doses may cause CNS effects.**
- **Benzathine penicillin only effective against extremely sensitive agents**
- **Certain species may be sensitive to procaine penicillin G**

Uses/Indications

Natural penicillins remain the drugs of choice for a variety of bacteria, including group A beta-hemolytic streptococci, many gram-positive anaerobes, spirochetes, gram-negative aerobic cocci, and some gram-negative aerobic bacilli. Generally, if a bacteria remains susceptible to a natural penicillin, either penicillin G or V is preferred for treating that infection as long as adequate penetration of the drug to the site of the infection occurs and the patient is not hypersensitive to penicillins.

Pharmacology/Actions

Penicillins 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