Uses/Indications
Ammonium molybdate and ammonium tetrathiomolybdate (TTM) are used for the investigational or compassionate treatment of copper poisoning in food animals, primarily sheep.

Adverse Effects
After apparent successful treatment for copper poisoning with ammonium tetrathiomolybdate (TTM), a flock of sheep became infertile, progressively unthrifty, and died 2–3 years later. The authors concluded the TTM was retained in the CNS, pituitary and adrenal glands and caused a toxic endocrinopathy (Haywood, Dincer et al. 2004).

Reproductive/Nursing Safety
In humans, the FDA categorizes this drug as category ***C*** for use during pregnancy (*Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans.*)

Doses
Note: In food animals, FARAD recommends a minimum 10 day preslaughter withdrawal time and a minimum 5 day milk withholding interval. (Haskell, Payne et al. 2005)

Ammonium tetrathiomolybdate does not go into solution readily and ammonium molybdate administered orally is often preferred.

SHEEP:

For treatment of copper poisoning:

a) Food animals: Ammonium molybdate: 200 mg per head PO once daily for 3 weeks. Ammonium tetrathiomolybdate: 1.7–3.4 mg per head IV or SC every other day for 3 treatments (Post and Keller 2000)

b) 100 mg with 1–gram sodium sulfate by mouth daily (Debuf 1991)

c) 200 mg ammonium or sodium molybdate plus 500 mg of sodium thiosulfate given daily PO for up to 3 weeks (Thompson and Buck 1993)

d) Ammonium tetrathiomolybdate: 1.7 mg/kg IV or 3.4 mg/kg SC every other day for 3 treatments. Alternatively, ammonium molybdate 50–500 mg PO once daily and sodium thiosulfate 300–1000 mg PO once daily for 3 weeks. (Plumlee 1996)

Dosage Forms/Regulatory Status/Synonyms
VETERINARY-LABELED PRODUCTS: None.

Note: Ammonium Molybdate or ammonium tetrathiomolybdate can be obtained from various chemical supply houses, but it is recommended to contact the FDA before treating for guidance when contemplating using molybdate.

HUMAN-LABELED PRODUCTS:

Ammonium Molybdate Injection: 25 mcg/mL (as 46 mcg/mL ammonium molybdate tetrahydrate) in 10 mL vial); *Molypen®* (American Pharmaceutical Partners); generic; (Rx)

Ammonium molybdate may also be known as: *Molybdene Injectable®*, or *Molypen®*. Ammonium tetrathiomolybdate may also be known as TTM.

AMOXICILLIN

(a-mox-i-***sill***-in) Amoxil®, Amoxi-Tabs®

AMINOPENICILLIN

Prescriber Highlights

- Bactericidal aminopenicillin with same spectrum as ampicillin (ineffective against bacteria that produce beta-lactamase)
- Most likely adverse effects are GI-related, but hypersensitivity & other adverse effects rarely occur
- Available in oral & parenteral dosage forms in USA

Uses/Indications
The aminopenicillins 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 Dosages section below.

Pharmacology/Actions
Like other penicillins, amoxicillin is a time-dependent, bactericidal (usually) agent that acts by inhibiting cell wall synthesis. Although there may be some slight differences in activity against certain organisms, amoxicillin generally shares the same spectrum of activity and uses as ampicillin. Because it is better absorbed orally (in nonruminants), higher serum levels may be attained than with ampicillin.

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 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.

In order to reduce the inactivation of penicillins by beta-lactamases, potassium clavulanate and sulbactam have been developed to inactivate these enzymes and thus extend the spectrum of those penicillins. When used with a 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 that are often associated with *E. coli,* Enterobacter, and Pseudomonas are not generally inhibited by clavulanic acid.

Pharmacokinetics

Amoxicillin trihydrate is relatively stable in the presence of gastric acid. After oral administration, it is about 74–92% absorbed in humans and monogastric animals. Food will decrease the rate, but not the extent of oral absorption and many clinicians suggest giving the drug with food, particularly if there is concomitant associated GI distress. Amoxicillin serum levels will generally be 1.5–3 times greater than those of ampicillin after equivalent oral doses.

After absorption, the volume of distribution for amoxicillin is approximately 0.3 L/kg in humans and 0.2 L/kg in dogs. The drug is widely distributed to many tissues, including liver, lungs, prostate (human), muscle, bile, and ascitic, pleural and synovial fluids. Amoxicillin will cross into the CSF when meninges are inflamed in concentrations that may range from 10–60% of those found in serum. Very low levels of the drug are found in the aqueous humor, and low levels found in tears, sweat and saliva. Amoxicillin crosses the placenta, but it is thought to be relatively safe to use during pregnancy. It is approximately 17–20% bound to human plasma proteins, primarily albumin. Protein binding in dogs is approximately 13%. Milk levels of amoxicillin are considered low.

Amoxicillin is eliminated primarily through renal mechanisms, principally by tubular secretion, but some of the drug is metabolized by hydrolysis to penicilloic acids (inactive) and then excreted in the urine. Elimination half-lives of amoxicillin have been reported as 45–90 minutes in dogs and cats, and 90 minutes in cattle. Clearance is reportedly 1.9 mL/kg/min in dogs.

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 penicillins, cephalosporins, or macrolides to rabbits, guinea pigs, chinchillas, hamsters, etc. or serious enteritis and clostridial enterotoxemia may occur.

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.

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, neutropenia, agranulocytosis, thrombocytopenia, leukopenia, anemias, lymphadenopathy, or full-blown anaphylaxis.

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

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

Reproductive/Nursing Safety

Penicillins have been shown to cross the placenta; safe use 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.*) In a separate system evaluating the safety of drugs in canine and feline pregnancy (Papich 1989), this drug is categorized as in class: ***A*** (*Probably safe. Although specific studies may not have proved the safety of all drugs in dogs and cats, there are no reports of adverse effects in laboratory animals or women.*)

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 amoxicillin and may be of significance in veterinary patients:

- **BACTERIOSTATIC ANTIMICROBIALS** (*e.g.*, **chloramphenicol, erythromycin** and other **macrolides, tetracyclines, sulfonamides,** etc.): Because there is evidence of *in vitro* antagonism between beta-lactam antibiotics and bacteriostatic antibiotics, use together has been generally not recommended, but actual clinical importance is not clear
- **METHOTREXATE**: Amoxicillin may decrease the renal excretion of MTX causing increased levels and potential toxic effects
- **PROBENECID**: Competitively blocks the tubular secretion of most penicillins, thereby increasing serum levels and serum half-lives

Laboratory Considerations

- Amoxicillin 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 amoxicillin.
- 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.

Doses

- **DOGS:**

For susceptible infections:

a) For Gram-positive infections: 10 mg/kg PO, IM, SC twice daily for at least 2 days after symptoms subside.

For Gram-negative infections: 20 mg/kg PO three times daily or IM, SC twice daily for at least 2 days after symptoms subside (Aucoin 2000)

b) For susceptible UTI's: 10–20 mg/kg PO q12h for 5–7 days.

For susceptible systemic infections (bacteremia/sepsis): 22–30 mg/kg IV, IM, SC q8h for 7 days.

For susceptible orthopedic infections: 22–30 mg/kg IV, IM, SC, or PO q6–8h for 7–10 days. (Greene, Hartmannn et al. 2006)

c) For Lyme disease: 22 mg/kg PO q12h for 21–28 days (Appel and Jacobson 1995)

■ **CATS:**

For susceptible infections:

a) For Gram-positive infections: 10 mg/kg PO, IM, SC twice daily for at least 2 days after symptoms subside.

For Gram-negative infections: 20 mg/kg PO three times daily or IM, SC twice daily for at least 2 days after symptoms subside (Aucoin 2000)

b) For susceptible UTI's and soft tissue infections: 50 mg (total dose per cat) or 11–22 mg/kg PO once daily for 5–7 days.

For sepsis: 10–20 mg/kg IV, SC, or PO q12h for as long as necessary. **Note:** Duration of treatment are general guidelines, generally treat for at least 2 days after all signs of infection are gone. (Greene, Hartmannn et al. 2006)

c) *C. perfringens*, bacterial overgrowth (GI): 22 mg/kg PO once daily for 5 days (Lappin 2000)

d) *C. perfringens* enterotoxicosis: 11–22 mg/kg PO two to three times daily for 7 days (Leib 2004a)

e) For treating *H. pylori* infections using triple therapy: amoxicillin 20 mg/kg PO twice daily for 14 days; metronidazole 10–15 mg/kg PO twice daily; clarithromycin 7.5 mg/kg PO twice daily (Simpson 2003b)

■ **FERRETS:**

For eliminating Helicobacter gastritis infections:

a) Using triple therapy: Metronidazole 22 mg/kg, amoxicillin 22 mg/kg and bismuth subsalicylate (original *Pepto-Bismol*®) 17.6 mg/kg PO. Give each 3 times daily for 3–4 weeks. (Hall 2000)

b) Using triple therapy: Metronidazole 20 mg/kg PO q12h, amoxicillin 20 mg/kg PO q12h and bismuth subsalicylate 17.5 mg/kg PO q8h. Give 21 days. Sucralfate (25 mg/kg PO q8h) and famotidine (0.5 mg/kg PO once daily) are also used. Fluids and assisted feeding should be continued while the primary cause of disease is investigated. (Johnson 2006c)

For susceptible infections:

a) 10–35 mg/kg PO or SC twice daily (Williams 2000)

■ **RABBITS/RODENTS/SMALL MAMMALS:**

Note: See warning above in Contraindications

a) Hedgehogs: 15 mg/kg IM or PO q12h (Smith 2000)

■ **CATTLE:**

For susceptible infections:

a) 6–10 mg/kg SC or IM q24h (Withdrawal time = 30 days) (Jenkins 1986)

b) For respiratory infections: 11 mg/kg IM or SC q12h (Hjerpe 1986), (Beech 1987b)

c) Calves: Amoxicillin trihydrate: 7 mg/kg PO q8–12h (Baggot 1983)

■ **HORSES:**

For susceptible infections:

a) For respiratory infections: 20–30 mg/kg PO q6h (Beech 1987b)

b) Foals: Amoxicillin Sodium: 15–30 mg/kg IV or IM q6–8h; amoxicillin trihydrate suspension: 25–40 mg/kg PO q8h; amoxicillin/clavulanate 15–25 mg/kg IV q6–8h (Brumbaugh 1999)

■ **BIRDS:**

For susceptible infections:

a) For most species: 150–175 mg/kg PO once to twice daily (using 50 mg/mL suspension) (Clubb 1986)

b) 100 mg/kg q8h PO (Bauck and Hoefer 1993)

c) 100 mg/kg q8h, IM, SC, PO (Hoeffer 1995)

d) Ratites: 15–22 mg/kg PO twice daily; in drinking water: 250 mg/gallon for 3–5 days (Jenson 1998)

■ **REPTILES:**

For susceptible infections:

a) For all species: 22 mg/kg PO q12–24h; not very useful unless used in combination with aminoglycosides (Gauvin 1993)

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

■ The oral suspension should preferably be refrigerated, but refrigeration is not absolutely necessary; any unused oral suspension should be discarded after 14 days

■ Amoxicillin may be administered orally without regard to feeding status

■ If the animal develops gastrointestinal symptoms (*e.g.*, vomiting, anorexia), giving with food may be of benefit

Chemistry/Synonyms

An aminopenicillin, amoxicillin is commercially available as the trihydrate. It occurs as a practically odorless, white, crystalline powder that is sparingly soluble in water. Amoxicillin differs structurally from ampicillin only by having an additional hydroxyl group on the phenyl ring.

Amoxicillin may also be known as: amoxycillin, p-hydroxyampicillin, or BRL 2333; many trade names are available.

Storage/Stability/Compatibility

Amoxicillin capsules, tablets, and powder for oral suspension should be stored at room temperature (15–30°C) in tight containers. After reconstitution, the oral suspension should preferably be refrigerated (refrigeration not absolutely necessary) and any unused product discarded after 14 days.

Dosage Forms/Regulatory Status/Withdrawal Times

VETERINARY-LABELED PRODUCTS:

Amoxicillin Oral Tablets: 50 mg, 100 mg, 150 mg, 200 mg, & 400 mg; *Amoxi-Tabs*® (Pfizer); (Rx). Approved for use in dogs and cats.

Amoxicillin Powder for Oral Suspension 50 mg/mL (after reconstitution) in 15 mL or 30 mL bottles; *Amoxi-Drop*® (Pfizer); (Rx). Approved for use in dogs and cats.

Amoxicillin Intramammary Infusion 62.5 mg/syringe in 10 mL syringes; *Amoxi-Mast*® (Schering-Plough); (Rx). Approved for use in lactating dairy cattle. Slaughter withdrawal (when administered as labeled) = 12 days; Milk withdrawal (when administered as labeled) = 60 hours.

HUMAN-LABELED PRODUCTS:

Amoxicillin Tablets (chewable) (as trihydrate): 125 mg, 200 mg, 250 mg, & 400 mg; *Amoxil*®(GlaxoSmithKline); generic; (Rx)

Amoxicillin Tablets (as trihydrate): 500 mg & 875 mg; *Amoxil*® (GlaxoSmithKline); generic; (Rx)

Amoxicillin Capsules (as trihydrate): 250 mg, & 500 mg; *Amoxil*® (GlaxoSmithKline); generic; (Rx)

Amoxicillin (as trihydrate) Powder for Oral Suspension: 50 mg/mL (in 15 and 30 mL bottles), 125 mg/5 mL in 80 mL & 150 mL; 200 mg/5 mL in 50 mL, 75 mL & 100 mL; 250 mg/5 mL in 80 mL, 100 mL & 150 mL; 400 mg/5 mL in 50 mL, 75 mL & 100 mL; *Amoxil*® &

Amoxil® Pediatric Drops (GlaxoSmithKline); (Apothecon), *Trimox®* (Sandoz); generic; (Rx)

Amoxicillin Tablets for Oral Suspension: 200 mg & 400 mg; *Dispermox®* (Ranbaxy); (Rx)

AMOXICILLIN/CLAVULANATE POTASSIUM AMOXICILLIN/CLAVULANIC ACID

(a-mox-i-***sill***-in clav-yue-***lan***-ate) Clavamox®, Augmentin®

POTENTIATED AMINOPENICILLIN

Prescriber Highlights

- Bactericidal aminopenicillin with beta-lactamase inhibitor that expands its spectrum. Not effective against Pseudomonas or Enterobacter
- Most likely adverse effects are GI related, but hypersensitivity & other adverse effects rarely occur

Uses/Indications

Amoxicillin/potassium clavulanate tablets and oral suspension products are approved for use in dogs and cats for the treatment of urinary tract, skin and soft tissue infections caused by susceptible organisms. It is also indicated for canine periodontal disease due to susceptible strains of bacteria.

Pharmacology/Actions

For information on the pharmacology/actions of amoxicillin, refer that monograph.

Clavulanic acid has only weak antibacterial activity when used alone and presently it is only available in fixed-dose combinations with either amoxicillin (oral) or ticarcillin (parenteral). Clavulanic acid acts by competitively and irreversibly binding to beta-lactamases, including types II, III, IV, and V, and penicillinases produced by Staphylococcus. Staphylococci that are resistant to penicillinase-resistant penicillins (*e.g.*, oxacillin) are considered resistant to amoxicillin/potassium clavulanate, although susceptibility testing may indicate otherwise. Amoxicillin/potassium clavulanate is usually ineffective against type I cephalosporinases. These plasmid-mediated cephalosporinases are often produced by members of the family Enterobacteriaceae, particularly *Pseudomonas aeruginosa*. When combined with amoxicillin, there is little if any synergistic activity against organisms already susceptible to amoxicillin, but amoxicillin-resistant strains (due to beta-lactamase inactivation) may be covered.

When performing Kirby-Bauer susceptibility testing, the *Augmentin®* (human-product trade name) disk is often used. Because the amoxicillin:clavulanic acid ratio of 2:1 in the susceptibility tests may not correspond to *in vivo* drug levels, susceptibility testing may not always accurately predict efficacy for this combination.

Pharmacokinetics

The pharmacokinetics of amoxicillin are presented in that drug's monograph. There is no evidence to suggest that the addition of clavulanic acid significantly alters amoxicillin pharmacokinetics. Clavulanate potassium is relatively stable in the presence of gastric acid and is readily absorbed. In dogs, the absorption half-life is reportedly 0.39 hours with peak levels occurring about 1 hour after dosing. Specific bioavailability data for dogs or cats was not located.

Clavulanic acid has an apparent volume of distribution of 0.32 L/kg in dogs and is distributed (with amoxicillin) into the lungs, pleural fluid and peritoneal fluid. Low concentrations of both drugs are found in the saliva, sputum and CSF (uninflamed meninges). Higher concentrations in the CSF are expected when meninges are inflamed, but it is questionable whether therapeutic levels are attainable. Clavulanic acid is 13% bound to proteins in dog serum. The drug readily crosses the placenta but is not believed to be teratogenic. Clavulanic acid and amoxicillin are both found in milk in low concentrations.

Clavulanic acid is apparently extensively metabolized in the dog (and rat) primarily to 1-amino-4-hydroxybutan-2-one. It is not known if this compound possesses any beta-lactamase inhibiting activity. The drug is also excreted unchanged in the urine via glomerular filtration. In dogs, 34–52% of a dose is excreted in the urine as unchanged drug and metabolites, 25–27% eliminated in the feces, and 16–33% into respired air. Urine levels of active drug are considered high, but may be only 1/5th of those of amoxicillin.

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.

Do not administer penicillins, cephalosporins, or macrolides to rabbits, guinea pigs, chinchillas, hamsters, etc. or serious enteritis and clostridial enterotoxemia may occur.

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, neutropenia, agranulocytosis, thrombocytopenia, leukopenia, anemias, lymphadenopathy, or full-blown anaphylaxis.

When given orally, penicillins may cause GI effects (anorexia, vomiting, diarrhea). Because the penicillins may 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.