Chemistry/Synonyms

A polyene macrolide antifungal agent produced by Streptomyces nodosus, amphotericin B occurs as a yellow to orange, odorless or practically odorless powder. It is insoluble in water and anhydrous alcohol. Amphotericin B is amphoteric and can form salts in acidic or basic media. These salts are more water soluble but possess less antifungal activity than the parent compound. Each mg of amphotericin B must contain not less than 750 micrograms of anhydrous drug. Amphotericin A may be found as a contaminant in concentrations not exceeding 5%. The commercially available powder for injection contains sodium desoxycholate as a solubilizing agent.

Newer lipid-based amphotericin B products are available that have less toxicity than the conventional desoxycholate form. These include amphotericin B cholesteryl sulfate complex (amphotericin B colloidal dispersion, ABCD, *Amphotec®*), amphotericin B lipid complex (ABLC, *Abelcet®*), and amphotericin B liposomal (ABL, L-AMB, *Ambisome®*).

Amphotericin B may also be known as: amphotericin; amphotericin B cholesteryl sulfate complex, amphotericin B lipid complex, amphotericin B liposome, amphotericin B phospholipid complex, amphotericin B-Sodium cholesteryl sulfate complex, anfotericina B, or liposomal amphotericin B; many trade names are available.

Storage/Stability/Compatibility

Vials of amphotericin B powder for injection should be stored in the refrigerator (2–8°C), protected from light and moisture. Reconstitution of the powder must be done with sterile water for injection (no preservatives—see directions for preparation in the Dosage Form section below).

After reconstitution, if protected from light, the solution is stable for 24 hours at room temperature and for 1 week if kept refrigerated. After diluting with D5W (must have pH >4.3) for IV use, the manufacturer recommends continuing to protect the solution from light during administration. Additional studies however, have shown that potency remains largely unaffected if the solution is exposed to light for 8–24 hours.

Amphotericin B deoxycholate is reportedly **compatible** with the following solutions and drugs: D5W, D5W in sodium chloride 0.2%, heparin sodium, heparin sodium with hydrocortisone sodium phosphate, hydrocortisone sodium phosphate/succinate and sodium bicarbonate.

Amphotericin B deoxycholate is reportedly **incompatible** with the following solutions and drugs: normal saline, lactated Ringer's, D5-normal saline, D5-lactated Ringer's, amino acids 4.25%–dextrose 25%, amikacin, calcium chloride/gluconate, carbenicillin disodium, chlorpromazine HCl, cimetidine HCl, diphenhydramine HCl, dopamine HCl, edetate calcium disodium (Ca EDTA), gentamicin sulfate, kanamycin sulfate, lidocaine HCl, metaraminol bitartrate, methyldopate HCl, nitrofurantoin sodium, oxytetracycline HCl, penicillin G potassium/sodium, polymyxin B sulfate, potassium chloride, prochlorperazine mesylate, streptomycin sulfate, tetracycline HCl, and verapamil HCl. 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:

Amphotericin B Desoxycholate Powder for Injection: 50 mg in vials; *Amphocin®* (Gensia Sicor); *Fungizone® Intravenous* (Apothecon); generic (Pharma-Tek); (Rx)

Directions for reconstitution/administration: Using strict aseptic technique and a 20 gauge or larger needle, rapidly inject 10 mL of sterile water for injection (without a bacteriostatic agent) directly into the lyophilized cake; immediately shake well until solution is clear. A 5 mg/mL colloidal solution results. Further dilute (1:50) for administration to a concentration of 0.1 mg/mL with 5% dextrose in water (pH >4.2). An in-line filter may be used during administration, but must have a pore diameter >1 micron.

Amphotericin B Lipid-Based Suspension for Injection: 100 mg/20 mL (as lipid complex) in 10 mL & 20 mL vials with 5 micron filter needles: *Abelcet®* (Enzon); (Rx)

Amphotericin B Lipid-Based Powder for Injection: 50 mg/vial (as cholesteryl) in 20 mL vials; 100 mg (as cholesteryl) in 50 mL vials; *Amphotec®* (Sequus Pharmaceuticals); 50 mg (as liposomal) in single-dose vials with 5-micron filter; *AmBisome®* (Fujisawa; (Rx)

Amphotericin B is also available in topical formulations: *Fungizone®* (Apothecon); (Rx)

AMPICILLIN
AMPICILLIN SODIUM
AMPICILLIN TRIHYDRATE

(am-pi-***sill***-in; sul-***bak***-tam) Polyflex®

AMINOPENICILLIN

Prescriber Highlights

- Bactericidal aminopenicillin with same spectrum as amoxicillin (ineffective against bacteria that produce beta-lactamase)
- Most likely adverse effects are GI-related, but hypersensitivity & other adverse effects rarely occur; may cause more GI effects than amoxicillin when used orally
- More susceptible than is amoxicillin to food reducing oral absorption
- Available in both parenteral & oral forms

Uses/Indications

In dogs and cats, ampicillin is not as well absorbed after oral administration as amoxicillin and its oral use has largely been supplanted by amoxicillin. It is used commonly in parenteral dosage forms when an aminopenicillin is indicated in all species.

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.

Pharmacology/Actions

Like other penicillins, ampicillin is a time-dependent, bactericidal (usually) agent that acts via inhibiting cell wall synthesis. Ampicillin and the other aminopenicillins 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 extend the spectrum of those penicillins. See the ampicillin/sulbactam or amoxicillin/clavulanate monographs for more information.

Pharmacokinetics

Ampicillin anhydrous and trihydrate are relatively stable in the presence of gastric acid. After oral administration, ampicillin is about 30–55% absorbed in humans (empty stomach) and monogastric animals. Food will decrease the rate and extent of oral absorption.

When administered parenterally (IM, SC) the trihydrate salt will achieve serum levels of approximately ½ those of a comparable dose of the sodium salt. The trihydrate parenteral dosage form should not be used where higher MIC's are required for treating systemic infections.

After absorption, the volume of distribution for ampicillin is approximately 0.3 L/kg in humans and dogs, 0.167 L/kg in cats, and 0.16–0.5 L/kg in cattle. The drug is widely distributed to many tissues, including liver, lungs, prostate (human), muscle, bile, and ascitic, pleural and synovial fluids. Ampicillin will cross into the CSF when meninges are inflamed in concentrations that may range from 10–60% those found in serum. Very low levels of the drug are found in the aqueous humor; low levels are found in tears, sweat and saliva. Ampicillin crosses the placenta, but is thought to be relatively safe to use during pregnancy. Ampicillin is approximately 20% bound to plasma proteins, primarily albumin. Milk levels of ampicillin are considered low. In lactating dairy cattle, the milk to plasma ratio is about 0.3.

Ampicillin 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 ampicillin have been reported as 45–80 minutes in dogs and cats, and 60 minutes in swine.

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.

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 manifest as rashes, fever, eosinophilia, neutropenia, 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.

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 ampicillin 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, particularly 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 ampicillin 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**: Ampicillin 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

- Ampicillin 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 ampicillin.
- 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: 10–20 mg/kg PO twice daily; 5 mg/kg IM, SC twice daily; 5 mg/kg IV three times daily

For Gram-negative infections: 20–30 mg/kg PO three times daily; 10 mg/kg IM, SC three times daily; 10 mg/kg IV four times daily (Aucoin 2000)

b) For susceptible UTI's: 12.5 mg/kg PO q12h for 3–7 days, 6.6 mg/kg IM or SC q12h for 3–7 days;

For susceptible soft tissue infections: 10–20 mg/kg PO, IM or SC q8h for 7 days;

For pneumonia, systemic: 22 mg/kg PO, IV or SC q8h for 7–14 days;

For meningitis, orthopedic infections: 22 mg/kg PO, IV, IM, SC q6–8h as long as necessary;

For susceptible sepsis, bacteremia: 20–40 mg/kg IV, IM or SC q6–8h for as long as necessary;

For neonatal sepsis: 50 mg/ kg IV or intraosseous q4–6h as long as necessary;

For susceptible orthopedic infections or meningitis: 22 mg/kg IV, IM, SC, or PO q6–8h for as long as necessary (Greene, Hartmannn et al. 2006)

c) For sepsis: 20–40 mg/kg IV q6–8h (Hardie 2000)

d) For susceptible UTI's: 25 mg/kg PO q8h (Polzin 2005c)

e) To eliminate the leptospiremic phase of leptospirosis: 22 mg/kg q6–8h IV during the acute illness until patient is eating, then amoxicillin 22 mg/kg PO q8h (Lunn 2006)

■ **CATS:**

For susceptible infections:

a) For Gram-positive infections: 10–20 mg/kg PO twice daily; 5 mg/kg IM, SC twice daily; 5 mg/kg IV three times daily;

For Gram-negative infections: 20–30 mg/kg PO three times daily; 10 mg/kg IM, SC three times daily; 10 mg/kg IV four times daily (Aucoin 2000)

b) For susceptible UTI's: 20 mg/kg PO q8–12h for 7–14 days;

For soft tissue infections 20–40 mg/kg PO q8–12h for 14 days;

For systemic infections: 7–11 mg/kg IV, IM or SC q8–12h for as long as necessary; (Greene, Hartmannn et al. 2006)

c) For sepsis: 20–40 mg/kg IV q6–8h (Hardie 2000)

■ **CATTLE:**

For susceptible infections:

a) For respiratory infections: Ampicillin trihydrate (*Polyflex*®): 22 mg/kg SC q12h (60 day slaughter withdrawal suggested) (Hjerpe 1986)

b) For respiratory infections: Ampicillin sodium 22 mg/kg SC q12h; Ampicillin trihydrate: 11 mg/kg IM q24h (Beech 1987b)

■ **HORSES:**

For susceptible infections:

a) Ampicillin sodium: 10–50 mg/kg IV or IM three times daily

Ampicillin trihydrate: 5–20 mg/kg IM twice daily (Robinson 1987)

Ampicillin sodium: 11–15 mg/IM or IV three to four times daily (Beech 1987a)

b) Foals: Ampicillin sodium 11 mg/kg q6h IM or IV (Furr 1999)

c) Foals: Ampicillin sodium 15–30 mg/kg IV or IM q 6–8h (Brumbaugh 1999)

d) For intrauterine infusion: 1–3 grams. Little science is available for recommending doses, volume infused, frequency diluents, etc. Most treatments are commonly performed every day or every other day for 3–7 days. (Perkins 1999)

■ **FERRETS:**

For susceptible infections: 5–10 mg/kg IM, SC or IV twice daily (Williams 2000)

■ **RABBITS/RODENTS/SMALL MAMMALS:**

a) Rabbits: Not recommended as it can cause a fatal enteritis (Ivey and Morrisey 2000)

b) Gerbils, Mice, Rats: 20–100 mg/kg PO, SC, IM q8–12h

c) Guinea pigs, Chinchillas, Hamsters: Do NOT use as it may cause enterocolitis (Adamcak and Otten 2000)

d) Hedgehogs: 10 mg/kg IM or PO once daily (Smith 2000)

■ **SWINE:**

For susceptible infections:

a) Ampicillin sodium: 6–8 mg/kg SC or IM q8h (Baggot 1983)

■ **BIRDS:**

For susceptible infections:

a) Amazon parrots: 150–200 mg/kg PO twice daily–three times daily (poorly absorbed PO); 100 mg/kg IM (as the trihydrate/*Polyflex*®) q4h.

Pet birds: 250 mg capsule in 8 oz. of drinking water (poorly absorbed; rapidly excreted)

Chickens: 1.65 g/L drinking water (see above)

Most birds: 250 mg/kg via feed for 5–10 days. Sprinkle on favorite food, or add to mash or corn mix. (Clubb 1986)

b) 100 mg/kg IM or IM q8h (Hoeffer 1995)

c) Ratites: 11–15 mg/kg PO or IV 3 times daily; 15–20 mg/kg IM twice daily (Jenson 1998)

■ **REPTILES:**

For susceptible infections:

a) All species: 3–6 mg/kg PO, SC or IM every 12–24 hours for 2 weeks; not very useful unless used in combination with aminoglycosides (Gauvin 1993)

b) For Chelonians (turtles et al): 50 mg/kg IM q12h (Jacobson 2000)

Monitoring

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

Client Information

■ Unless otherwise instructed by the veterinarian, this drug should be given orally on an empty stomach, at least 1 hour before feeding or 2 hours after.

■ Keep oral suspension in the refrigerator and discard any unused suspension after 14 days. If stored at room temperature, discard unused suspension after 7 days.

Chemistry/Synonyms

A semi-synthetic aminopenicillin, ampicillin anhydrous and trihydrate occur as practically odorless, white, crystalline powders that are slightly soluble in water. At usual temperatures (<42°C), ampicillin anhydrous is more soluble in water than the trihydrate (13 mg/mL vs. 6 mg/mL at 20°C). Ampicillin anhydrous or trihydrate oral suspensions have a pH of 5–7.5 after reconstitution with water.

Ampicillin sodium occurs as an odorless or practically odorless, white to off-white, crystalline hygroscopic powder. It is very

soluble in water or other aqueous solutions. After reconstitution, ampicillin sodium has a pH of 8–10 at a concentration of 10 mg/mL. Commercially available ampicillin sodium for injection has approximately 3 mEq of sodium per gram of ampicillin.

Potency of the ampicillin salts is expressed in terms of ampicillin anhydrous.

Ampicillin may also be known as: aminobenzylpenicillin, ampicillinum, ampicillinum anhydricum, anhydrous ampicillin, AY-6108, BRL-1341, NSC-528986, or P-50; many trade names are available.

Storage/Stability/Compatibility

Ampicillin anhydrous or trihydrate capsules and powder for oral suspension should be stored at room temperature (15–30°C). After reconstitution, the oral suspension is stable for 14 days if refrigerated (2–8°C); 7 days when kept at room temperature.

Ampicillin trihydrate for injection (*Polyflex*®) is stable for 12 months if refrigerated (2–8°C); 3 months when kept at room temperature.

Ampicillin sodium for injection is relatively unstable after reconstitution and should generally be used within 1 hour of reconstitution. As the concentration of the drug in solution increases, the stability of the drug decreases. Dextrose may also speed the destruction of the drug by acting as a catalyst in the hydrolysis of ampicillin.

While most sources recommend using solutions of ampicillin sodium immediately, studies have demonstrated that at concentrations of 30 mg/mL, ampicillin sodium solutions are stable up to 48 hours at 4°C in sterile water for injection or 0.9% sodium chloride (72 hours if concentrations are 20 mg/mL or less). Solutions with a concentration of 30 mg/mL or less have been shown to be stable up to 24 hours in solutions of lactated Ringer's solution if kept at 4°C. Solutions of 20 mg/mL or less are reportedly stable up to 4 hours in D_5W if refrigerated.

Ampicillin sodium is reportedly **compatible** with the following additives (see the above paragraph for more information): heparin sodium, chloramphenicol sodium succinate, procaine HCl and verapamil HCl.

Ampicillin sodium is reportedly **incompatible** with the following additives: amikacin sulfate, chlorpromazine HCl, dopamine HCl, erythromycin lactobionate, gentamicin HCl, hydralazine HCl, hydrocortisone sodium succinate, kanamycin sulfate, lincomycin HCl, oxytetracycline HCl, polymyxin B sulfate, prochlorperazine edisylate, sodium bicarbonate and tetracycline HCl. 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:

Ampicillin Trihydrate Injection Powder for Suspension: 10 g and 25 g (of ampicillin) vials; *Polyflex*® (Fort Dodge); (Rx). Approved for use in dogs, cats, and cattle. Withdrawal times at labeled doses (cattle; do not treat for more than 7 days): Milk = 48 hours; Slaughter = 6 days (144 hours).

HUMAN-LABELED PRODUCTS:

Ampicillin Sodium Powder for Injection: 250 mg, 500 mg, 1 g, & 2 g in vials; generic; (Rx)

Ampicillin Capsules (as trihydrate): 250 mg, & 500 mg; *Principen*® (Geneva); generic; (Rx)

Ampicillin (as the trihydrate) Powder for Oral Suspension: 125 mg/5 mL & 250 mg/5 mL when reconstituted in 100 mL and 200 mL; *Principen*® (Geneva); (Rx)

AMPICILLIN SODIUM + SULBACTAM SODIUM

(am-pi-***sill***-in; sul-***bak***-tam) Unasyn®

INJECTABLE POTENTIATED AMINOPENICILLIN

Prescriber Highlights

- Parenteral potentiated aminopenicillin that may be used for infections where amoxicillin/clavulanate would be appropriate but when an injectable antibiotic is required
- Hypersensitivity reactions possible; contraindicated in patients with documented severe hypersensitivity to penicillins
- Usually dosed IM or IV q6–8h

Uses/Indications

Ampicillin sodium/sulbactam sodium in a 2:1 ratio is effective when used parenterally for several types of infections caused by many beta-lactamase-producing bacterial strains of otherwise resistant *E. coli*, *Pasturella* spp., *Staphylococcus* spp., *Klebsiella*, and *Proteus*. Other aerobic bacteria commonly susceptible to this combination include *Streptococcus*, *Listeria monocytogenes*, *Bacillus anthracis*, *Salmonella*, *Pasturella*, and *Acinetobacter*. Anaerobic bacterial infections caused by *Clostridium*, *Bacteroides*, *Fusobacterium*, *Peptostreptococcus* or *Propionibacterium* may be effectively treated with ampicillin/sulbactam.

Type I beta-lactamases that may be associated with *Citrobacter*, *Enterobacter*, *Serratia* and *Pseudomonas* are not generally inhibited by sulbactam or clavulanic acid. Ampicillin/sulbactam is ineffective against practically all strains of *Pseudomonas aeruginosa*.

In dogs and cats, ampicillin/sulbactam therapy may be considered when oral amoxicillin/clavulanate treatment is not viable (patient NPO, critically ill) or when large parenteral doses would be desirable (sepsis, pneumonia, other severe infections) for treating susceptible bacterial infections or prophylaxis.

Ampicillin/sulbactam has been used successfully to treat experimentally induced *Klebsiella* pneumonia in foals.

Pharmacology/Actions

When sulbactam is combined with ampicillin it extends its spectrum of activity to those bacteria that produce beta-lactamases of Richmond-Sykes types II-VI that would otherwise render ampicillin ineffective. Sulbactam binds to beta-lactamases thereby "protecting" the beta-lactam ring of ampicillin from hydrolysis.

Sulbactam has some intrinsic antibacterial activity against some bacteria (*Neisseria*, *Moraxella*, *Bacteroides*) at achievable levels. Sulbactam binding to certain penicillin-binding proteins (PBPs) may explain its activity. For most bacteria, sulbactam alone does not achieve levels sufficient to act alone as an antibacterial but when used in combination with ampicillin, synergistic effects may result.

On a mg for mg basis, clavulanic acid is a more potent beta-lactamase inhibitor than is sulbactam, but sulbactam has advantages of reduced likelihood of inducing chromosomal beta-lactamases, greater tissue penetration and greater stability.

For further information on the pharmacology of ampicillin, refer to that monograph.