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.

Reproductive/Nursing Safety

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-clavulanate 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

Note: All doses are for combined quantities of both drugs (unless noted otherwise).

- **DOGS:**

  For susceptible infections:

  a) 13.75 mg/kg PO twice daily; do not exceed 30 days of therapy (Package insert; *Clavamox*®—Pfizer)

  b) For susceptible UTI's: 12.5 mg/kg PO q12h for 5–7 days

  For susceptible skin, soft tissue infections: 12.5 mg/kg PO q12h for 5–7 days (may need to extend to 21 days; do not exceed past 30 days). Much higher doses have been recommended for resistant skin infections.

  For susceptible deep pyodermas: 12.5 mg/kg PO q12h for 14–120 days

  For systemic bacteremia: 22 mg/kg PO q8–12h for 7 days

  Note: Duration of treatments are general guidelines; generally treat for at least 2 days after all signs of infection are gone. (Greene, Hartmannn et al. 2006)

  c) For Gram-positive infections: 10 mg/kg PO twice daily

  For Gram-negative infections: 20 mg/kg PO three times daily (Aucoin 2000)

  d) For non-superficial pyoderma: 10–25 mg/kg PO twice daily for 3–6 weeks. Maximum dose is 650 mg twice daily. Increase to three times daily if no response in 1 week. If no response by the 2nd week, discontinue. (Aucoin 2002a)

  e) For recurrent pyoderma: 13.75–22 mg/kg PO q8–12h (Hillier 2006b)

- **CATS:**

  For susceptible infections:

  a) 62.5 mg PO twice daily; do not exceed 30 days of therapy (Package insert; *Clavamox*®—Pfizer)

  b) For Gram-positive infections: 10 mg/kg PO twice daily;

  For Gram-negative infections: 20 mg/kg PO three times daily (Aucoin 2000)

  c) For susceptible UTI's: 62.5 mg/cat (total dose) PO q12h for 10–30 days;

  For susceptible skin, soft tissue infections: 62.5 mg/cat (total dose) or 10–20 mg/kg PO q12h for 5–7 days;

  For susceptible sepsis, pneumonia: 10–20 mg/kg PO q8h for 7–10 days

  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)

- **FERRETS:**

  For susceptible infections:

  a) 10–20 mg/kg PO 2–3 times daily (Williams 2000)

- **BIRDS:**

  For susceptible infections:

  a) 50–100 mg/kg PO q6–8h (Hoeffer 1995)

  b) Ratites: 10–15 mg/kg PO twice daily (Jenson 1998)

Client Information

- The oral suspension should preferably be refrigerated, but refrigeration is not absolutely necessary; any unused oral suspension should be discarded after 10 days
- Amoxicillin/clavulanate 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

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 performed with these agents.

Chemistry/Synonyms

A beta-lactamase inhibitor, clavulanate potassium occurs as an off-white, crystalline powder that has a pK_a of 2.7 (as the acid) and is very soluble in water and slightly soluble in alcohol at room temperatures. Although available in commercially available preparations as the potassium salt, potency is expressed in terms of clavulanic acid.

Amoxicillin may also be known as: amoxycillin, p-hydroxyampicillin, or BRL 2333; many trade names are available. Clavulanate potassium may also be known as: clavulanic acid, BRL-14151K, or kalii clavulanas.

Storage/Stability/Compatibility

Clavulanate products should be stored at temperatures less than 24°C (75°F) in tight containers. Potassium clavulanate is reportedly very susceptible to moisture and should be protected from excessive humidity.

After reconstitution, oral suspensions are stable for 10 days when refrigerated. Unused portions should be discarded after that time. If kept at room temperature, suspensions are reportedly stable for 48 hours. The veterinary oral suspension should be reconstituted by adding 14 mL of water and shaking vigorously; refrigerate and discard any unused portion after 10 days.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Oral Tablets (4:1 ratio):

62.5 mg: Amoxicillin 50 mg/12.5 mg clavulanic acid (as the potassium salt)

125 mg: Amoxicillin 100 mg/25 mg clavulanic acid (as the potassium salt)

250 mg: Amoxicillin 200 mg/50 mg clavulanic acid (as the potassium salt)

375 mg: Amoxicillin 300 mg/75 mg clavulanic acid (as the potassium salt); *Clavamox Tablets*® (Pfizer); (Rx). Approved for use in dogs and cats.

Powder for Oral Suspension:

Amoxicillin 50 mg/12.5 mg clavulanic acid (as the potassium salt) per mL in 15 mL dropper bottles; C*lavamox® Drops* (Pfizer); (Rx). Approved for use in dogs and cats.

HUMAN-LABELED PRODUCTS:

Note: Human-labeled amoxicillin/clavulanate products have varying ratios of amoxicillin:clavulanate ranging from 2:1 to 7:1.

Amoxicillin (as trihydrate)/Clavulanic Acid (as potassium salt) Tablets: Amoxicillin 250 mg/125 mg clavulanic acid; Amoxicillin 500 mg/125 mg clavulanic acid; Amoxicillin 875 mg/125 mg clavulanic acid; *Augmentin*® (GlaxoSmithKline); generic (Rx)

Chewable Tablets: Amoxicillin 125 mg/31.25 mg clavulanic acid; Amoxicillin 200 mg/28.5 mg clavulanic acid; 250 mg/62.5 mg clavulanic acid & 400 mg/57 mg clavulanic acid; *Augmentin*® (GlaxoSmithKline); generic; (Rx)

Powder for Oral Suspension—Amoxicillin/Clavulanic Acid (as potassium salt) after reconstitution: Amoxicillin 125 mg/31.25 mg clavulanic acid per 5 mL in 75 mL, 100 mL & 150 mL; Amoxicillin 200 mg/28.5 mg clavulanic acid per 5 mL in 50 mL, 75 mL &100 mL; Amoxicillin 250 mg/62.5 mg clavulanic acid per 5 mL in 75 mL, 100 mL & 150 mL; Amoxicillin 400 mg/57 mg clavulanic acid per 5 mL in 50 mL, 75 mL & 100 mL; 600 mg/42.9 mg clavulanic acid per 5 mL in 75 mL, 100 mL, 125 mL & 200 mL; *Augmentin*® & *Augmentin ES-600*® (GlaxoSmithKline); *Amoclan*® (West-ward); generic; (Rx)

AMPHOTERICIN B DESOXYCHOLATE AMPHOTERICIN B LIPID-BASED

(am-foe-***ter***-i-sin ***bee***) Abelcet®, Fungizone®

ANTIFUNGAL

Prescriber Highlights

- Systemic antifungal used for serious mycotic infections
- Must be administered IV
- Nephrotoxicity is biggest concern, particularly with the deoxycholate form; newer lipid based products are less nephrotoxic & penetrate into tissues better, but are more expensive
- Renal function monitoring essential
- Drug interactions

Uses/Indications

Because the potential exists for severe toxicity associated with this drug, it should only be used for progressive, potentially fatal fungal infections. Veterinary use of amphotericin has been primarily in dogs, but other species have been treated successfully. For further information on fungal diseases treated, see the Pharmacology and Dosage sections.

The liposomal form of amphotericin B can be used to treat Leishmaniasis.

Pharmacology/Actions

Amphotericin B is usually fungistatic, but can be fungicidal against some organisms depending on drug concentration. It acts by binding to sterols (primarily ergosterol) in the cell membrane and alters the permeability of the membrane allowing intracellular potassium and other cellular constituents to "leak out." Because bacteria and rickettsia do not contain sterols, amphotericin B has no activity against those organisms. Mammalian cell membranes do contain sterols (primarily cholesterol) and the drug's toxicity may be a result of a similar mechanism of action, although amphotericin binds less strongly to cholesterol than ergosterol.

Amphotericin B has *in vitro* activity against a variety of fungal organisms, including Blastomyces, Aspergillus, Paracoccidioides, Coccidioides, Histoplasma, Cryptococcus, Mucor, and Sporothrix. Zygomycetes is reportedly variable in its response to amphotericin. Aspergillosis in dogs and cats does not tend to respond satisfactorily to amphotericin therapy. Additionally, amphotericin B has *in vivo* activity against some protozoa species, including *Leishmania* spp. and *Naegleria* spp.

It has been reported that amphotericin B has immunoadjuvant properties but further work is necessary to confirm the clinical significance of this effect.

Pharmacokinetics

Pharmacokinetic data on veterinary species is apparently unavailable. In humans (and presumably animals), amphotericin B is poorly absorbed from the GI tract and must be given parenterally to achieve sufficient concentrations to treat systemic fungal infections. After intravenous injection, the drug reportedly penetrates well into most tissues but does not penetrate well into the pancreas, muscle, bone, aqueous humor, or pleural, pericardial, synovial, and