Storage/Stability
Compounded capsules should be stored in child-resistant, tight containers protected from light. Until further stability studies can be performed, capsules should be stored in the freezer.

Aqueous solutions are reportedly not very stable. It is recommended that fresh solutions using the 10% powder for addition to drinking water (used for pigeons) be freshly prepared every day.

Dosage Forms/Regulatory Status
VETERINARY-LABELED PRODUCTS:

None in the USA; a 10% ronidazole powder to be added to drinking water for treating Trichomonas infections in pigeons is available in some countries, but these products are unsuitable for use in cats due to the dosage required and the unpalatability (very bitter) of the powder and solution. Capsules prepared from 100% bulk powder for an individual feline patient should be obtained from a compounding pharmacy that can prepare the capsules in a bio-safety hood that will protect the compounder from drug exposure.

The FDA prohibits this drug for use in food animals.

HUMAN-LABELED PRODUCTS: None

S-ADENOSYL-METHIONINE (SAMe) ADEMETIONINE

(***ess***-ah-***den***-oh-seel meth-***ie***-oh-neen)

HEPATOPROTECTANT

Prescriber Highlights
- "Nutraceutical" that can be used as an adjunctive treatment for liver disease (chronic hepatitis), osteoarthritis, or treatment of acetaminophen toxicity in small animals
- Well tolerated
- Not a regulated drug; choose products carefully

Uses/Indications
In small animal medicine, SAMe is most commonly used as an adjunctive treatment for liver disease (chronic hepatitis, hepatic lipidosis, cholangiohepatitis, feline triad disease, etc.). It may also be of benefit in osteoarthritis, treatment of acute hepatotoxin-induced liver toxicity (*e.g.*, acetaminophen toxicity), and at-risk patients on long-term therapy using drugs with hepatotoxic potential.

In humans, SAMe is being used as a treatment for depression, osteoarthritis, AIDS-related myopathy, intrahepatic cholestasis, liver disease, alcoholic liver cirrhosis, fibromyalgia, adult ADHD, Alzheimer's, migraines, etc.

Pharmacology/Actions
S-adenosyl-methionine (SAMe) is an endogenous molecule synthesized by cells throughout the body. SAMe is formed from the amino acid methionine and ATP, in conjunction with SAMe synthetase enzyme (an enzyme manufactured in the liver, a rate-limiting step in the presence of liver compromise). SAMe is an essential part of three major biochemical pathways: transmethylation, transsulfuration, and aminopropylation. Normal function of these pathways is especially vital to the liver as many metabolic reactions occur there. In the transmethylation pathway, SAMe serves as a methyl donor (necessary for many substances and drugs to be activated and/or eliminated). Transmethylation is essential in phospholipid synthesis important to cell membrane structure, fluidity, and function. In aminopropylation, SAMe donates aminopropyl groups and is a source of polyamines. Aminopropylation is important in producing substances that have antiinflammatory effects, protein and DNA synthesis, and promoting cell replication and liver mass regeneration. In transulfuration, SAMe generates sulfur containing compounds important for conjugation reactions used in detoxification and as a precursor to glutathione (GSH). Glutathione is important in many metabolic processes and cell detoxification. The conversion of SAMe to glutathione requires the presence of folate, cyanocobalamin (B_{12}), and pyridoxine (B_6). Normally, the liver produces ample SAMe, but in liver disease or in the presence of hepatotoxic substances, endogenous conversion to glutathione may be deficient. Exogenous SAMe has been shown to increase liver and red cell glutathione levels and/or prevent its depletion. SAMe inhibits apoptosis secondary to alcohol or bile acids in hepatocytes.

In humans, the mechanism for its antidepressant effects are not well understood, but it apparently increases serotonin turnover and increases dopamine and norepinephrine levels. Neuroimaging studies in humans show that SAMe affects the brain similarly to other antidepressant medications.

Pharmacokinetics
Oral bioavailability is dependent on the salt used to stabilize SAMe. Oral bioavailability of the tosylate salt is reportedly 1% whereas the 1,4-butanedisulfonate form has a bioavailability of 5%. The presence of food in the gut can substantially reduce the amount of drug absorbed. Peak levels occur in 1–6 hours after oral dosing. Once absorbed, SAMe enters the portal circulation and is primarily metabolized in the liver. In humans, 17% of a dose of radio-labeled SAMe was recovered in the urine within 48 hours of dosing; 27% in the feces.

Contraindications/Precautions/Warnings
There are no apparent contraindications to the use of SAMe.

Adverse Effects
Adverse effects appear to be minimal or non-existent in treated animals. Most studies in humans have shown adverse effects similar to that of placebo. Oral SAMe in humans may cause anorexia, nausea, vomiting, diarrhea, flatulence, constipation, dry mouth, insomnia/nervousness, headache, sweating, and dizziness.

Reproductive/Nursing Safety
The safety of exogenous SAMe has not been proven in pregnancy; use with caution. Limited studies in laboratory animals and in pregnant women with liver disease have not demonstrated any ill effects to mother or fetus.

It is unknown if SAMe enters maternal milk.

Overdosage/Acute Toxicity
SAMe appears to be quite safe. LD_{50} in rodents exceeds 4.65 g/kg, and toxicity studies in dogs and cats at the usual prescribed dosages demonstrated no deleterious effects. In the case of an overdose, gastrointestinal effects may be observed, but unlikely to require treatment.

Drug Interactions
No interactions have been documented, but theoretically, concurrent use of SAMe with **tramadol, meperidine, dextromethorphan, pentazocine,** monoamine oxidase inhibitors (**MAOIs**) including **selegiline**, selective serotonin reuptake inhibitors (**SSRIs**) such as **fluoxetine**, or other antidepressants (*e.g.*, **amitriptyline, clomipramine**) could cause additive serotonergic effects.

Laboratory Considerations
No specific laboratory interactions or considerations noted.

Doses
■ **DOGS & CATS:**

Daily dose for animals with body weights of:
up to 12 pounds (5.5 kg): one 90 mg tablet;
12–25 pounds (5.5–11 kg): two 90 mg tablets (or one 225 mg tablet, if more convenient);
25–35 pounds (11–16 kg): one 225 mg tablet;
35–65 pounds (16–29.5 kg): two 225 mg tablets;
65–90 pounds (29.5 kg–41 kg): three 225 mg tablets;
over 90 pounds (41 kg+): four 225 mg tablets.

Daily dosage may also be calculated based on 18 mg/kg of body weight and rounded to the closest tablet size or combination of sizes. Product should be given on an empty stomach, at least one hour before feeding. If giving more than one tablet, may divide total daily dosage and give twice daily. The number of tablets can be gradually reduced or may be increased at any time depending on the pet's needs. (Package information; *Denosyl*®—Nutramax)

For Liver Disease:

a) For adjunctive treatment of chronic hepatitis: Dogs: 17–20 mg/kg or higher per day given on an empty stomach
Cats: 200 mg/day on an empty stomach.
Recommend using a reliable product with proven research in dogs and cats such as *Denosyl*®. (Center 2002)

b) 20 mg/kg once daily (Willard 2006b)

Monitoring
- Clinical signs (appetite, activity, attitude)
- Liver enzymes, bilirubin, bile acids
- Liver biopsies
- Hepatic and erythrocyte glutathione levels (available at research institutions only at this time); may require 1–4 months before any changes in lab values are noted

Client Information
- Administer tablets to animal with an empty stomach, preferably at least one hour before feeding
- Keep tablets in original packaging until administration. Do not crush or split tablets

Chemistry/Synonyms
S-adenosyl-methionine (SAMe) is a naturally occurring molecule found throughout the body. Because pure SAMe is highly reactive and unstable, commercially available forms of SAMe are salt forms; sulfate, sulfate-p-toluenesulfonate (also known as tosylate), and butanedisulfonate salts can all be procured.

SAMe may also be known as: S-adenosyl-L-methionine, S-adenosylmethionine, SAM, SAM-e, adenosylmethionine, Sammy, methioninyl adenylate, *Donamet*®, *Gumbaral*®, *Isimet*®, *MoodLift*®, *S Amet*®, *Samyr*®, *Transmetil*®, and *Tunik*®.

Storage/Stability
Unless otherwise labeled, SAMe tablets should be stored at room temperature. Avoid conditions of high temperature or humidity. SAMe is inherently unstable in acidic or aqueous environments; store in tightly sealed, moisture-resistant containers.

Dosage Forms/Regulatory Status
VETERINARY-LABELED PRODUCTS:

None as a pharmaceutical. SAMe is considered a nutritional supplement by the FDA. No standards have been accepted for potency, purity, safety, or efficacy by regulatory bodies. Supplements are available from a wide variety of sources and dosage forms include tablets in a variety of concentrations. There are specific products marketed for use in animals, including *Denosyl*® (Nutramax) in 90 mg, 225 mg, & 425 mg enteric-coated, blister-packed tablets and *Zentonil*® (Vetoquinol) in 100 mg, 200 mg and 400 mg tablets. Bioequivalence between SAMe products is not assured. A combination product *Denamarin*® (Nutramax), containing SAMe and silybin (silymarin) is also labeled for use in dogs and cats.

HUMAN-LABELED PRODUCTS:

None as a pharmaceutical.

SALINE/HYPEROSMOTIC LAXATIVES MAGNESIUM SALTS PEG 3350 PRODUCTS

GoLYTELY®, Epsom Salts

LAXATIVES

Prescriber Highlights
- **Saline/hyperosmotic agents for constipation, bowel "cleansing", & to increase elimination of GI toxins**
- **Contraindications: PEG 3350 solutions are contraindicated in patients with GI obstruction, gastric retention, bowel perforation, toxic colitis, or megacolon. Saline cathartics should be used with extreme caution in patients with renal insufficiency, pre-existing water-balance or electrolyte abnormalities, or cardiac disease.**
- **Adverse Effects: Cramping, nausea possible**
- **If magnesium salts used chronically: Hypermagnesemia (muscle weakness, ECG changes & CNS effects)**
- **Drug Interactions**

Uses/Indications
The saline laxatives are used for their cathartic action to relieve constipation. They are also used to reduce intestinal transit time thereby reducing the absorption of orally ingested toxicants. Polyethylene glycol 3350 balanced electrolyte solutions are used to evacuate the colon prior to intestinal examination or surgery.

Pharmacology/Actions
Although unproven, it is commonly believed that the hyperosmotic effect of the poorly absorbed magnesium cation causes water retention, stimulates stretch receptors and enhances peristalsis in the small intestine and colon. Recent data, however, suggests that magnesium ions may directly decrease transit times and increase cholecystokinin release.

Polyethylene glycol 3350 is a non-absorbable compound that acts as an osmotic agent. By adding sodium sulfate as the primary sodium source, sodium absorption is minimized. Other electrolytes (bicarbonate potassium and chloride) are also added so that no net