carbonate. While the drug does not directly reduce urine pH, by reducing ammonia and bicarbonate production by urease-producing bacteria, it prevents increases in urine pH. The drug may act synergistically with several antimicrobial agents (*e.g.*, carbenicillin, gentamicin, clindamycin, trimethoprim-sulfa or chloramphenicol) in treating some urinary tract infections. The drug's effects on urinary pH and infection also indirectly inhibit the formation of urinary calculi (struvite, carbonate-apatite).

Pharmacokinetics
No canine specific data was located. In humans, the drug is rapidly absorbed after PO administration. Absolute bioavailability "in animals" is reported to be 50–60%. AHA is well distributed throughout body fluids. It is partially metabolized to acetamide, which is active; 36–65% of a dose is excreted in the urine unchanged, and 9–14% excreted in the urine as acetamide. The remainder is reportedly excreted as CO_2 via the respiratory tract.

Contraindications/Precautions/Warnings
AHA is contraindicated in patients with poor renal function (*e.g.*, serum creatinine >2.5 mg/dl) or when it is not specifically indicated (see Indications).

Acetohydroxamic acid is reportedly very toxic in cats and should not be used in felines.

Adverse Effects
In dogs, GI effects (anorexia, vomiting, mouth/esophageal ulcers), hemolytic anemia, hyperbilirubinemia and bilirubinuria have been reported. Other potential adverse effects include: CNS disturbances (anxiety, depression, tremulousness), hematologic effects (reticulocytosis, bone marrow depression), phlebitis, and skin rashes/alopecia. Effects on bilirubin metabolism have also been reported.

Reproductive/Nursing Safety
AHA use is considered contraindicated during pregnancy. In pregnant beagles, doses of 25 mg/kg/day caused cardiac, coccygeal, and abdominal wall abnormalities in puppies. At high doses (>750 mg/kg) leg deformities have been noted in test animals. Higher doses (1500 mg/kg) caused significant encephalopathologies. In humans, the FDA categorizes this drug as category ***X*** for use during pregnancy (*Studies in animals or humans demonstrate fetal abnormalities or adverse reaction; reports indicate evidence of fetal risk. The risk of use in pregnant women clearly outweighs any possible benefit.*)

Overdosage/Acute Toxicity
In humans, mild overdoses have resulted in hemolysis after several weeks of treatment, particularly in patients with reduced renal function. Acute overdoses are expected to cause clinical signs such as anorexia, tremors, lethargy, vomiting and anxiety. Increased reticulocyte counts and a severe hemolytic reaction are laboratory findings that would be expected. Treatment for an acute overdose may include intensive hematologic monitoring with adjunctive supportive therapy, including possible transfusions.

Drug Interactions
The following drug interactions have either been reported or are theoretical in humans or animals receiving acetohydroxamic acid (AHA) and may be of significance in veterinary patients:

- **IRON:** AHA may chelate iron salts in the gut if given concomitantly
- **METHENAMINE:** AHA may have a synergistic effect with methenamine in inhibiting the urine pH increases caused by urease-producing *Proteus* spp.; AHA may also potentiate the antibacterial effect of methenamine against these bacteria
- **ALCOHOL:** In humans, AHA with alcohol has resulted in rashes

Laboratory Considerations
- Although AHA is a true urease inhibitor, it apparently does not interfere with urea nitrogen determination using one of the following: urease-Berthelot, urease-glutamate dehydrogenase or diacetyl monoxime methods.

Doses
- **DOGS:**

  For adjunctive therapy of persistent struvite uroliths and persistent urease-producing bacteria after treating with antibiotics and calculolytic diets:

  a) 12.5 mg/kg twice daily PO (Osborne, Lulich et al. 1993); (Lulich, Osborne et al. 2000)

Monitoring
- CBC
- Renal/Hepatic (bilirubin) function
- Efficacy

Client Information
- This medication can cause several adverse effects in dogs; contact veterinarian if dog develops persistent or severe vomiting, has a lack of appetite, a change in urine color, develops yellowing of the whites of the eyes, or has decreased energy/activity.

Chemistry/Synonyms
An inhibitor of urease, acetohydroxamic acid occurs as a white crystal having a pKa of 9.32–9.4 and a pH of about 9.4. 850 mg are soluble in one mL of water, and 400 mg are soluble in one mL of alcohol.

Acetohydroxamic acid may also be known as: AHA, Acetic acid oxime, N-Acetylhydroxylamide, N-Hydroxyacetamide, *Lithostat*® or *Uronefrex*®.

Storage/Stability
Tablets should be stored in tight containers.

Dosage Forms/Regulatory Status
VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Acetohydroxamic Acid Tablets: 250 mg; *Lithostat*® (Mission); (Rx)

ACETYLCYSTEINE

(assah-teel-*sis*-tay-een) N-acetylcysteine, Mucomyst®, NAC

ANTIDOTE; MUCOLYTIC

Prescriber Highlights
- **Used primarily as a treatment for acetaminophen or phenol toxicity & for its mucolytic effect; used anecdotally for treating degenerative myelopathy**
- **Also used as a topical ophthalmic (see the Topical Ophthalmic section in the appendix)**
- **Has caused hypersensitivity & bronchospasm when used in pulmonary tree**
- **Administer via gastric- or duodenal tube for acetaminophen poisoning in animals**

Uses/Indications

Acetylcysteine is used in veterinary medicine as both a mucolytic agent in the pulmonary tree and as a treatment for acetaminophen or phenol toxicity in small animals. It has been used anecdotally with aminocaproic acid to treat degenerative myelopathy in dogs.

In horses with strangles, acetylcysteine instilled into the gutteral pouch has been used to help break up chondroids and avoid the need for surgical removal. Acetylcysteine enemas have been used in neonatal foals to break up meconium refractory to repeated enemas.

Pharmacology/Actions

When administered into the pulmonary tree, acetylcysteine reduces the viscosity of both purulent and nonpurulent secretions and expedites the removal of these secretions via coughing, suction, or postural drainage. The free sulfhydryl group on the drug is believed to reduce disulfide linkages in mucoproteins; this effect is most pronounced at a pH from 7–9. The drug has no effect on living tissue or fibrin.

Acetylcysteine can reduce the extent of liver injury or methemoglobinemia after ingestion of acetaminophen or phenol, by providing an alternate substrate for conjugation with the reactive metabolite of acetaminophen, thus maintaining or restoring glutathione levels.

Pharmacokinetics

When given orally, acetylcysteine is absorbed from the GI tract. When administered via nebulization or intratracheally into the pulmonary tract, most of the drug is involved in the sulfhydryl-disulfide reaction and the remainder is absorbed. Absorbed drug is converted (deacetylated) into cysteine in the liver and then further metabolized.

Contraindications/Precautions/Warnings

Acetylcysteine is contraindicated (for pulmonary indications) in animals hypersensitive to it. There are no contraindications for its use as an antidote.

Because acetylcysteine may cause bronchospasm in some patients when used in the pulmonary system, animals with bronchospastic diseases should be monitored carefully when using this agent.

Adverse Effects

When given orally for acetaminophen toxicity, acetylcysteine can cause GI effects (nausea, vomiting) and rarely, urticaria. Because the taste of the solution is very bad, use of taste masking agents (*e.g.*, colas, juices) have been used. Since oral dosing of these drugs may be very difficult in animals, gastric or duodenal tubes may be necessary.

Rare adverse effects reported when acetylcysteine is administered into the pulmonary tract, include: hypersensitivity, chest tightness, bronchoconstriction, and bronchial or tracheal irritation.

Reproductive/Nursing Safety

Reproduction studies in rabbits and rats have not demonstrated any evidence of teratogenic or embryotoxic effects when used in doses up to 17 times normal. 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.*)

It is unknown if acetylcysteine enters milk. Use caution when administering to a nursing dam.

Overdosage/Acute Toxicity

The LD_{50} of acetylcysteine in dogs is 1 g/kg (PO) and 700 mg/kg (IV). It is believed that acetylcysteine is quite safe (with the exception of the adverse effects listed above) in most overdose situations.

Drug Interactions

- **ACTIVATED CHARCOAL:** The use of activated charcoal as a gut adsorbent of acetaminophen is controversial, as charcoal may also adsorb acetylcysteine. Because cats can develop methemoglobinemia very rapidly after ingestion of acetaminophen, do not delay acetylcysteine treatment and preferably give the first dose intravenously. If using the solution (not labeled for injectable use), it is preferable to use a 0.2 micron in-line filter.

Doses

- **DOGS:**

For acetaminophen toxicity:

a) A 2–3 hour wait between activated charcoal and PO administration of acetylcysteine (NAC) is necessary. Give NAC as an initial oral loading dose of 140 mg/kg (dilute to 5% in dextrose or sterile water), followed by 70 mg/kg PO four times daily (q6h) for 7 treatments. With ingestion of massive quantities, some authors suggest using a 280 mg/kg loading dose and continuing treatment for 12–17 doses. May also be given IV after diluting to 5% and given via slow IV over 15–20 minutes. Additional therapy may include IV fluids, blood or *Oxyglobin®*, ascorbic acid and SAMe. (Wismer 2006a)

b) 150 mg/kg PO or IV initially, then 50 mg/kg q4h for 17 additional doses (Bailey 1986a)

c) Loading dose of 140 mg/kg PO, then 70 mg/kg PO every 6 hours for 7 treatments (Grauer and Hjelle 1988a)

For phenol toxicity:

a) 140 mg/kg PO or IV initially, then 50 mg/kg q4h for 3 days. May be partially effective to reduce hepatic and renal injury. Resultant methemoglobinemia should be treated with ascorbic acid or methylene blue. (Dorman and Dye 2005)

For respiratory use:

a) 50 mL/hr for 30–60 minutes every 12 hours by nebulization (Kirk 1986)

For degenerative myelopathy:

a) 25 mg/kg PO q8h for 2 weeks, then q8h every other day. The 20% solution should be diluted to 5% with chicken broth or suitable diluent. Used in conjunction with aminocaproic acid (500 mg per dog PO q8h indefinitely). Other treatments may include prednisone (0.25–0.5 mg/kg PO daily for 10 days then every other day), Vitamin C (1000 mg PO q12h) and Vitamin E (1000 Int. Units PO q12h). **Note:** No treatment has been shown to be effective in published trials. (Shell 2003a)

- **CATS:**

For acetaminophen toxicity:

a) A 2–3 hour wait between activated charcoal and PO administration of acetylcysteine (NAC) is necessary. Give NAC as an initial oral loading dose of 140 mg/kg (dilute to 5% in dextrose or sterile water), followed by 70 mg/kg PO four times daily (q6h) for 7 treatments. With ingestion of massive quantities, some authors suggest using a 280 mg/kg loading dose and continuing treatment for 12–17 doses. May also be given IV after diluting to 5% and given via slow IV over 15–20 minutes. Additional therapy may include IV fluids, blood or *Oxyglobin®*, ascorbic acid and SAMe. (Wismer 2006a)

b) 150 mg/kg PO or IV initially, then 50 mg/kg q4h for 17 additional doses (Bailey 1986a)

For phenol toxicity:

a) 140 mg/kg PO or IV initially, then 50 mg/kg q4h for 3 days. May be partially effective to reduce hepatic and renal injury. Resultant methemoglobinemia should be treated with ascorbic acid or methylene blue. (Dorman and Dye 2005)

For respiratory use:

a) 50 mL/hr for 30–60 minutes every 12 hours by nebulization (Kirk 1986)

For adjunctive treatment of hepatic lipidosis (see also Carnitine):

a) Identify underlying cause of anorexia and provide a protein replete feline diet, give acetylcysteine (NAC) at 140 mg/kg IV over 20 minutes, then 70 mg/kg IV q12h; dilute 10% NAC with saline 1:4 and administer IV using a 0.25 micron filter; correct hypokalemia and hypophosphatemia, beware of electrolyte changes with re-feeding phenomenon (Center 2006c)

■ **HORSES:**

To help break up chondroids in the gutteral pouch:

a) Instill 20% solution (Foreman 1999)

In neonatal foals to break up meconium refractory to repeated enemas:

a) 8 grams in 20 g sodium bicarbonate in 200 mL water (pH of 7.6), give as enema as needed to effect (Freeman 1999)

b) With foal in lateral recumbency, insert a 30 french foley catheter with a 30 cc bulb for a retention enema. Using gravity flow, infuse slowly 100–200 mL of 4% acetylcysteine solution and retain for 30–45 minutes. IV fluids and pain medication should be considered. Monitor for possible bladder distention. (Pusterla, Magdesian et al. 2003)

Monitoring

When used for acetaminophen poisoning:

■ Hepatic enzymes (particularly in dogs)
■ Acetaminophen level, if available (particularly in dogs)
■ Hemogram, with methemoglobin value (particularly in cats)
■ Serum electrolytes, hydration status

Client Information

■ This agent should be used in a clinically supervised setting only

Chemistry/Synonyms

The N-acetyl derivative of L-cysteine, acetylcysteine occurs as a white, crystalline powder with a slight acetic odor. It is freely soluble in water or alcohol.

Acetylcysteine may also be known as: N-acetylcysteine or N-acetyl-L-cysteine, NAC, 5052 acetylcysteinum, NSC-111180, *Acetadote®, Mucomyst®* or *ACC®*.

Storage/Stability/Compatibility

When unopened, vials of sodium acetylcysteine should be stored at room temperature (15–30°C). After opening, vials should be kept refrigerated and used within 96 hours. The product labeled for IV use states to use within 24 hours.

Acetylcysteine is **incompatible** with oxidizing agents; solutions can become discolored and liberate hydrogen sulfide when exposed to rubber, copper, iron, and during autoclaving. It does not react to aluminum, stainless steel, glass or plastic. If the solution becomes light purple in color, potency is not appreciably affected, but it is best to use non-reactive materials when giving the drug via nebulization. Acetylcysteine solutions are **incompatible** with amphotericin B, ampicillin sodium, erythromycin lactobionate, tetracycline, oxytetracycline, iodized oil, hydrogen peroxide and trypsin.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Acetylcysteine injection: 20% (200 mg/mL), (0.5 mg/mL EDTA in 30 mL single-dose vials, preservative free; *Acetadote®* (Cumberland); (Rx)

Acetylcysteine Solution: 10% & 20% (as sodium) in 4 mL, 10 mL, 30 mL & 100 mL (20% only) vials; *Mucomyst®* (Apothecon); (Rx) **Note:** If using this product for dilution and then intravenous dosing, it is preferable to use a 0.2 micron in-line filter.

Acetylsalicylic Acid — See Aspirin

ACITRETIN

(ase-a-*tre*-tin) Soriatane®

RETINOID

Note: Originally etretinate was used for certain dermatologic indications in small animals (primarily dogs). It has been withdrawn from the market and replaced with acitretin, an active metabolite of etretinate with the same indications, but a much shorter half-life. Much of the information below is extrapolated from etretinate data.

Prescriber Highlights

- Retinoid that may be useful for certain dermatologic conditions in small animals
- Contraindications: Pregnancy; Caution: Cardiovascular disease, hypertriglyceridemia or sensitivity to retinoids
- Adverse Effects: Limited experience; appears to be fairly well tolerated in small animals Potentially: anorexia/vomiting/diarrhea, cracking of foot pads, pruritus, ventral abdominal erythema, polydipsia, lassitude, joint pain/stiffness, eyelid abnormalities & conjunctivitis (KCS), swollen tongue, & behavioral changes
- Known teratogen; do not use in households with pregnant women present (Plumb's recommendation)
- May be very expensive; may need to compound smaller capsules for small dogs or cats
- Drug-drug; drug-lab interactions

Uses/Indications

Acitretin may be useful in the treatment of canine lamellar ichthyosis, solar-induced precancerous lesions in Dalmatians or bull Terriers, actinic keratoses, squamous cell carcinomas, and intracutaneous cornifying epitheliomas (multiple keratoacanthomas).

While the drug has provided effective treatment of idiopathic seborrhea (particularly in cocker spaniels), it is not effective in treating the ceruminous otitis that may also be present. Results have been disappointing in treating idiopathic seborrheas seen in basset hounds and West Highland terriers.

Acitretin's usage in cats is very limited, but etretinate has shown some usefulness in treating paraneoplastic actinic keratosis, solar-induced squamous cell carcinoma and Bowen's Disease in this species.

Pharmacology/Actions

Acitretin is a synthetic retinoid agent potentially useful in the treatment of several disorders related to abnormal keratinization and/