Client Information

- This compound is recommended for use by veterinary professionals only
- Clients should be made aware of the "investigational" nature of using acemannan systemically; adverse effects are possible

Chemistry

Acemannan is a complex carbohydrate polymer that is derived from Aloe vera. It is a long-chained polydispersed beta-(1,4)-acetylated polymannose with interspersed *O*-acetyl groups with a mannose: acetyl ratio of approximately 1:1.

Storage/Stability

Acemannan injection should be stored at temperatures less than 35°C (95°F); protect from extremes of heat or light.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Acemannan 10 mg vial with 10 mL vial of diluent (sterile saline) in kits of two vials (one of each) or eight vials (4 of each): *Acemannan Immunostimulant*® (VPL); OTC Biologic. Labeled for use in dogs or cats. **Note:** This product is a USDA-licensed biologic and is not an FDA-approved product.

Note: There are also topical products labeled for veterinary use that contain acemannan including a wound dressing and cleansing foam. Trade name is *CarraVet*® (VPL).

HUMAN-LABELED PRODUCTS: No systemic products located

ACEPROMAZINE MALEATE

(ase-***pro***-ma-zeen) PromAce®, Aceproject®

PHENOTHIAZINE SEDATIVE/TRANQUILIZER

Prescriber Highlights

- Negligible analgesic effects
- Dosage may need to be reduced in debilitated or geriatric animals, those with hepatic or cardiac disease, or when combined with other agents
- Inject IV slowly; do not inject into arteries
- Certain dog breeds (*e.g.*, giant breeds, sight hounds) may be overly sensitive to effects
- May cause significant hypotension, cardiac rate abnormalities, hypo- or hyperthermia
- May cause penis protrusion in large animals (esp. horses)

Uses/Indications

Acepromazine is approved for use in dogs, cats, and horses. Labeled indications for dogs and cats include: ". . . as an aid in controlling intractable animals . . . alleviate itching as a result of skin irritation; as an antiemetic to control vomiting associated with motion sickness" and as a preanesthetic agent. The use of acepromazine as a sedative/tranquilizer in the treatment of adverse behaviors in dogs or cats has largely been supplanted by newer, effective agents that have fewer adverse effects. Its use for sedation during travel is controversial and many no longer recommend drug therapy for this purpose.

In horses, acepromazine is labeled ". . . as an aid in controlling fractious animals," and in conjunction with local anesthesia for various procedures and treatments. It is also commonly used in horses as a pre-anesthetic agent at very small doses to help control behavior.

Although not approved, it is used as a tranquilizer (see doses) in other species such as swine, cattle, rabbits, sheep and goats. Acepromazine has also been shown to reduce the incidence of halothane-induced malignant hyperthermia in susceptible pigs.

Pharmacology/Actions

Acepromazine is a phenothiazine neuroleptic agent. While the exact mechanisms of action are not fully understood, the phenothiazines block post-synaptic dopamine receptors in the CNS and may also inhibit the release of, and increase the turnover rate of dopamine. They are thought to depress portions of the reticular activating system that assists in the control of body temperature, basal metabolic rate, emesis, vasomotor tone, hormonal balance, and alertness. Additionally, phenothiazines have varying degrees of anticholinergic, antihistaminic, antispasmodic, and alpha-adrenergic blocking effects.

The primary desired effect for the use of acepromazine in veterinary medicine is its tranquilizing action. Additional pharmacologic actions that acepromazine possess, include antiemetic, antispasmodic, and hypothermic actions. Some researchers have reported that acepromazine has anticonvulsant activity, but in veterinary medicine it is generally felt that phenothiazines should not be used in epileptic animals or those susceptible to seizures (*e.g.*, post-myelography) as it may precipitate seizures.

Acepromazine may decrease respiratory rates, but studies have demonstrated that little or no effect occurs with regard to the blood gas picture, pH or oxyhemoglobin saturation. A dose dependent decrease in hematocrit is seen within 30 minutes after dosing in horses and dogs. Hematocrit values in horses may decrease up to 50% of pre-dose values; this is probably due to increased splenic sequestration of red cells.

Besides lowering arterial blood pressure in dogs, acepromazine causes increases in central venous pressure, a vagally induced bradycardic effect and transient sinoatrial arrest. The bradycardia may be negated by a reflex tachycardic effect secondary to decreases in blood pressure. Acepromazine also has antidysrhythmic effects. Acepromazine has been demonstrated to inhibit the arrhythmias induced by ultra-short acting barbiturates, and protect against the ventricular fibrillatory actions of halothane and epinephrine. Other pharmacologic actions are discussed in the adverse effects section below.

Pharmacokinetics

The pharmacokinetics of acepromazine have been studied in the horse (Ballard et al. 1982). The drug has a fairly high volume of distribution (6.6 L/kg), and is more than 99% protein bound. The onset of action is fairly slow, requiring up to 15 minutes following IV administration, with peak effects seen in 30–60 minutes. The elimination half-life in horses is approximately 3 hours.

Acepromazine is metabolized in the liver with both conjugated and unconjugated metabolites eliminated in the urine. Metabolites may be found in equine urine up to 96 hours after dosing.

Contraindications/Precautions/Warnings

Animals may require lower dosages of general anesthetics following acepromazine. Use cautiously and in smaller doses in animals with hepatic dysfunction, cardiac disease, or general debilitation. Because of its hypotensive effects, acepromazine is relatively contraindicated in patients with hypovolemia or shock. Phenothiazines are relatively contraindicated in patients with tetanus or strychnine intoxication due to effects on the extrapyramidal system.

Intravenous injections should be made slowly. Do not administer intra-arterially in horses since it may cause severe CNS excitement/

depression, seizures and death. Because of its effects on thermoregulation, use cautiously in very young or debilitated animals.

Acepromazine has no analgesic effects; treat animals with appropriate analgesics to control pain. The tranquilization effects of acepromazine can be overridden and it cannot always be counted upon when used as a restraining agent. Do not administer to racing animals within 4 days of a race.

In dogs, acepromazine's effects may be individually variable and breed dependent. Dogs with MDR1 mutations (many Collies, Australian shepherds, etc.) may develop a more pronounced sedation that persists longer than normal. It may be prudent to reduce initial doses by 25% to determine the reaction of a patient identified or suspected of having this mutation.

Acepromazine should be used very cautiously as a restraining agent in aggressive dogs as it may make the animal more prone to startle and react to noises or other sensory inputs. In geriatric patients, very low doses have been associated with prolonged effects of the drug. Giant breeds and greyhounds may be extremely sensitive to the drug while terrier breeds are somewhat resistant to its effects. Atropine may be used with acepromazine to help negate its bradycardic effects.

In addition to the legal aspects (not approved) of using acepromazine in cattle, the drug may cause regurgitation of ruminal contents when inducing general anesthesia.

Adverse Effects

Acepromazine's effect on blood pressure (hypotension) is well described and an important consideration in therapy. This effect is thought to be mediated by both central mechanisms and through the alpha-adrenergic actions of the drug. Cardiovascular collapse (secondary to bradycardia and hypotension) has been described in all major species. Dogs may be more sensitive to these effects than other animals.

In male large animals acepromazine may cause protrusion of the penis; in horses, this effect may last 2 hours. Stallions should be given acepromazine with caution as injury to the penis can occur with resultant swelling and permanent paralysis of the penis retractor muscle. Other clinical signs that have been reported in horses include excitement, restlessness, sweating, trembling, tachypnea, tachycardia and, rarely, seizures and recumbency.

Its effects of causing penis extension in horses, and prolapse of the membrana nictitans in horses and dogs, may make its use unsuitable for show animals. There are also ethical considerations regarding the use of tranquilizers prior to showing an animal or having the animal examined before sale.

Occasionally an animal may develop the contradictory clinical signs of aggressiveness and generalized CNS stimulation after receiving acepromazine. IM injections may cause transient pain at the injection site.

Reproductive/Nursing Safety

In humans, the FDA categorizes phenothiazines 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.*) In a separate system evaluating the safety of drugs in canine and feline pregnancy (Papich 1989), this drug is categorized as in class: ***B*** (*Safe for use if used cautiously. Studies in laboratory animals may have uncovered some risk, but these drugs appear to be safe in dogs and cats or these drugs are safe if they are not administered when the animal is near term.)*

Overdosage/Acute Toxicity

The LD_{50} in mice is 61 mg/kg after IV dosage and 257 mg/kg after oral dose. Dogs receiving 20–40 mg/kg over 6 weeks apparently demonstrated no adverse effects. Dogs gradually receiving up to 220 mg/kg orally exhibited signs of pulmonary edema and hyperemia of internal organs, but no fatalities were noted.

There were 128 exposures to acepromazine maleate reported to the ASPCA Animal Poison Control Center (APCC; www.apcc.aspca.org) during 2005–2006. In these cases, 89 were dogs with 37 showing clinical signs and the remaining 39 reported cases were cats with 12 cats showing clinical signs. Common findings in dogs recorded in decreasing frequency included ataxia, lethargy, sedation, depression, and recumbency. Common findings in cats recorded in decreasing frequency included lethargy, hypothermia, ataxia, protrusion of the third eyelid, and anorexia.

Because of the apparent relatively low toxicity of acepromazine, most overdoses can be handled by monitoring the animal and treating clinical signs as they occur; massive oral overdoses should definitely be treated by emptying the gut if possible. Hypotension should not be treated with epinephrine; use either phenylephrine or norepinephrine (levarterenol). Seizures may be controlled with barbiturates or diazepam. Doxapram has been suggested as an antagonist to the CNS depressant effects of acepromazine.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving acepromazine or other phenothiazines and may be of significance in veterinary patients:

- **ACETAMINOPHEN:** Possible increased risk for hypothermia
- **ANTACIDS:** May cause reduced GI absorption of oral phenothiazines
- **ANTIDIARRHEAL MIXTURES** (*e.g.*, **Kaolin/pectin, bismuth subsalicylate mixtures**): May cause reduced GI absorption of oral phenothiazines
- **CNS DEPRESSANT AGENTS** (**barbiturates, narcotics, anesthetics**, etc.): May cause additive CNS depression if used with acepromazine
- **EPINEPHRINE:** Phenothiazines block alpha-adrenergic receptors; concomitant epinephrine can lead to unopposed beta-activity causing vasodilation and increased cardiac rate
- **OPIATES:** May enhance the hypotensive effects of acepromazine; dosages of acepromazine are generally reduced when used with an opiate
- **ORGANOPHOSPHATE AGENTS:** Acepromazine should not be given within one month of worming with these agents as their effects may be potentiated
- **PHENYTOIN:** Metabolism may be decreased if given concurrently with phenothiazines
- **PROCAINE:** Activity may be enhanced by phenothiazines
- **PROPRANOLOL:** Increased blood levels of both drugs may result if administered with phenothiazines
- **QUINIDINE:** With phenothiazines may cause additive cardiac depression

Doses

Note: The manufacturer's dose of 0.5–2.2 mg/kg for dogs and cats is considered by many clinicians to be 10 times greater than is necessary for most indications. Give IV doses slowly; allow at least 15 minutes for onset of action.

- **DOGS:**
  a) Premedication: 0.03–0.05 mg/kg IM or 1–3 mg/kg PO at least one hour prior to surgery (not as reliable) (Hall and Clarke 1983)
  b) Restraint/sedation: 0.025–0.2 mg/kg IV; maximum of 3 mg or 0.1–0.25 mg/kg IM; Preanesthetic: 0.1–0.2 mg/kg IV or IM; maximum of 3 mg; 0.05–1 mg/kg IV, IM or SC (Morgan 1988)

c) To reduce anxiety in the painful patient (not a substitute for analgesia): 0.05 mg/kg IM, IV or SC; do not exceed 1 mg total dose (Carroll 1999)
d) 0.55–2.2 mg/kg PO or 0.55–1.1 mg/kg IV, IM or SC (Package Insert; *PromAce*®—Fort Dodge)
e) As a premedicant with morphine: acepromazine 0.05 mg/kg IM; morphine 0.5 mg/kg IM (Pablo 2003b)

■ **CATS:**

a) Restraint/sedation: 0.05–0.1 mg/kg IV, maximum of 1 mg (Morgan 1988)
b) To reduce anxiety in the painful patient (not a substitute for analgesia): 0.05 mg/kg IM, IV or SC; do not exceed 1 mg total dose (Carroll 1999)
c) 1.1–2.2 mg/kg PO, IV, IM or SC (Package Insert; *PromAce*®—Fort Dodge)
d) 0.11 mg/kg with atropine (0.045–0.067 mg/kg) 15–20 minutes prior to ketamine (22 mg/kg IM). (Booth 1988a)

■ **FERRETS:**

a) As a tranquilizer: 0.25–0.75 mg/kg IM or SC; has been used safely in pregnant jills, use with caution in dehydrated animals. (Finkler 1999)
b) 0.1–0.25 mg/kg IM or SC; may cause hypotension/hypothermia (Williams 2000)

■ **RABBITS/RODENTS/SMALL MAMMALS:**

a) Rabbits: As a tranquilizer: 1 mg/kg IM, effect should begin in 10 minutes and last for 1–2 hours (Booth 1988a)
b) Rabbits: As a premed: 0.1–0.5 mg/kg SC; 0.25–2 mg/kg IV, IM, SC 15 minutes prior to induction. No analgesia; may cause hypotension/hypothermia. (Ivey and Morrisey 2000)
c) Mice, Rats, Hamsters, Guinea pigs, Chinchillas: 0.5 mg/kg IM. Do not use in Gerbils. (Adamcak and Otten 2000)

■ **CATTLE:**

a) Sedation: 0.01–0.02 mg/kg IV or 0.03–0.1 mg/kg IM (Booth 1988a)
b) 0.05–0.1 mg/kg IV, IM or SC (Howard 1986)
c) Sedative one hour prior to local anesthesia: 0.1 mg/kg IM (Hall and Clarke 1983)

■ **HORSES:** (**Note:** ARCI UCGFS Class 3 Drug)

a) For mild sedation: 0.01–0.05 mg/kg IV or IM. Onset of action is about 15 minutes for IV; 30 minutes for IM (Taylor 1999)
b) 0.044–0.088 mg/kg (2–4 mg/100 lbs. body weight) IV, IM or SC (Package Insert; *PromAce*®—Fort Dodge)
c) 0.02–0.05 mg/kg IM or IV as a preanesthetic (Booth 1988a)
d) Neuroleptanalgesia: 0.02 mg/kg given with buprenorphine (0.004 mg/kg IV) or xylazine (0.6 mg/kg IV) (Thurmon and Benson 1987)
e) For adjunctive treatment of laminitis (developmental phase): 0.066–0.1 mg/kg 4–6 times per day (Brumbaugh, Lopez et al. 1999)

■ **SWINE:**

a) 0.1–0.2 mg/kg IV, IM, or SC (Howard 1986)
b) 0.03–0.1 mg/kg (Hall and Clarke 1983)
c) For brief periods of immobilization: acepromazine 0.5 mg/kg IM followed in 30 minutes by ketamine 15 mg/kg IM. Atropine (0.044 mg/kg IM) will reduce salivation and bronchial secretions. (Lumb and Jones 1984)

■ **SHEEP & GOATS:**

a) 0.05–0.1 mg/kg IM (Hall and Clarke 1983)

Monitoring

- Cardiac rate/rhythm/blood pressure if indicated and possible to measure
- Degree of tranquilization
- Male horses should be checked to make sure penis retracts and is not injured
- Body temperature (especially if ambient temperature is very hot or cold)

Client Information

- May discolor the urine to a pink or red-brown color; this is not abnormal
- Acepromazine is approved for use in dogs, cats, and horses not intended for food

Chemistry/Synonyms

Acepromazine maleate (formerly acetylpromazine) is a phenothiazine derivative that occurs as a yellow, odorless, bitter tasting powder. One gram is soluble in 27 mL of water, 13 mL of alcohol, and 3 mL of chloroform.

Acepromazine Maleate may also be known as: acetylpromazine maleate, "ACE", ACP, *Aceproject*®, *Aceprotabs*®, *PromAce*®, *Plegicil*®, *Notensil*®, and *Atravet*®.

Storage/Stability/Compatibility

Store protected from light. Tablets should be stored in tight containers. Acepromazine injection should be kept from freezing.

Although controlled studies have not documented the compatibility of these combinations, acepromazine has been mixed with atropine, buprenorphine, chloral hydrate, ketamine, meperidine, oxymorphone, and xylazine. Both glycopyrrolate and diazepam have been reported to be physically **incompatible** with phenothiazines, however, glycopyrrolate has been demonstrated to be **compatible** with promazine HCl for injection.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Acepromazine Maleate for Injection: 10 mg/mL for injection in 50 mL vials; *Aceproject*® (Butler), *PromAce*® (Fort Dodge); generic; (Rx). Approved forms available for use in dogs, cats and horses not intended for food.

Acepromazine Maleate Tablets: 5, 10 & 25 mg in bottles of 100 and 500 tablets; *PromAce*® (Fort Dodge); *Aceprotabs*® (Butler) generic; (Rx). Approved forms available for use in dogs, cats and horses not intended for food.

When used in an extra-label manner in food animals, it is recommended to use the withdrawal periods used in Canada: Meat: 7 days; Milk: 48 hours. Contact FARAD (see appendix) for further guidance.

The ARCI (Racing Commissioners International) has designated this drug as a class 3 substance. See the appendix for more information.

HUMAN-LABELED PRODUCTS: None