cause of the chances for accidental percutaneous absorption of potentially toxic compounds, the admixing of DMSO with other compounds is not to be done casually.

Dosage Forms/Regulatory Status

VETERINARY APPROVED PRODUCTS:

Dimethyl Sulfoxide Veterinary Gel 90%: *Domoso® Gel* (Fort Dodge) 90% (medical grade) in 60 g, and 120 g tubes, and 425 g containers. Labeled for use in dogs and horses. Do not administer to horses that are to be slaughtered for food.

Dimethyl Sulfoxide Veterinary Solution 90%: *Domoso® Solution* (Fort Dodge) 90% (medical grade) in 1 pint and 1 gallon bottles. Labeled for use in canines and equines. Do not administer to horses that are to be slaughtered for food.

The ARCI (Racing Commissioners International) has designated this drug as a class 5 substance. See the appendix for more information.

HUMAN APPROVED PRODUCTS:

Dimethylsulfoxide Solution: 50 % aqueous solution in 50 mL; *Rimso-50®* (Research Industries); Dimethyl Sulfoxide (Bioniche); (Rx)

Note: A topical otic product, *Synotic®* (Fort Dodge) that contains: DMSO 60% and fluocinolone acetonide 0.01% is also available for veterinary use. Supplied in 8 mL and 60 mL dropper bottles.

DINOPROST TROMETHAMINE PROSTAGLANDIN F2ALPHA TROMETHAMINE

(***dye***-noe-prost) Lutalyse®

PROSTAGLANDIN

Prescriber Highlights

- (THAM) salt of the naturally occurring prostaglandin F2alpha used as a luteolytic agent for estrous synchronization, pyometra treatment, & as an abortifacient
- Contraindications: Pregnancy (when abortion or induced parturition not wanted); manufacturer lists several contraindications for horses
- Extreme caution in elderly or debilitated animals
- Do NOT administer IV
- Pregnant women should not handle; humans with asthma & women of childbearing age should handle with caution
- Adverse effects (DOGS/CATS): Abdominal pain, emesis, defecation, urination, pupillary dilation followed by constriction, tachycardias, restlessness & anxiety, fever, hypersalivation, dyspnea & panting; fatalities possible (esp. dogs)
- Adverse Effects: (CATTLE): Infection at injection site, salivation, & hyperthermia possible
- Adverse Effects (SWINE): Erythema & pruritus, urination, defecation, slight ataxia, hyperpnea, dyspnea, nesting behavior, abdominal muscle spasms, tail movements, increased vocalization & salivation
- Adverse Effects (HORSES): Body temperature changes/sweating; seen less frequently: increased respiratory & heart rates, ataxia, abdominal pain, & lying down

Uses/Indications

Lutalyse® (Upjohn) is labeled for use in cattle as a luteolytic agent for estrous synchronization, unobserved (silent) estrous in lactating dairy cattle, pyometra, and as an abortifacient in feedlot and non–lactating dairy cattle. It is labeled in swine to act as a parturient inducing agent. The product is labeled for use in mares as a luteolytic agent to control the time of estrus in cycling mares and to assist in inducing estrus in "difficult to breed mares."

Unlabeled uses of dinoprost include its use in small animals as an abortifacient agent and as adjunctive medical therapy in pyometra. Although not approved, dinoprost is used also in sheep and goat reproductive medicine.

Pharmacology/Actions

Prostaglandin F2alpha has several pharmacologic effects on the female reproductive system, including stimulation of myometrial activity, relaxation of the cervix, and inhibition of steroidogenesis by corpora lutea; can potentially lyse corpora lutea.

Pharmacokinetics

In studies done in rodents, dinoprost was demonstrated to distribute very rapidly to tissues after injection. In cattle, the serum half-life of dinoprost has been stated to be only "minutes" long.

Contraindications/Precautions/Warnings

Unless being used as an abortifacient or parturition inducer, dinoprost should not be used during pregnancy in all species. Dinoprost is contraindicated in animals with bronchoconstrictive respiratory disease (*e.g.*, asthma, "heavey" horses). It should not be administered intravenously.

According to the manufacturer, dinoprost is contraindicated in mares with acute or subacute disorders of the vascular system, GI tract, respiratory system, or reproductive tract.

Dinoprost should be used with extreme caution, if at all, in dogs or cats greater than 8 years old, or with preexisting cardiopulmonary or other serious disease (liver, kidney, etc.). Some clinicians regard closed-cervix pyometra as a relative contraindication to the use of dinoprost.

Adverse Effects

In cattle, increased temperature has been reported when administered in overdose (5–10X recommended doses) quantities. Limited salivation and bacterial infections at the injection site have been reported. If administered intravenously, increased heart rates have been noted.

In mares, transient decreased body (rectal) temperature and sweating have been reported most often. Less frequently, increased respiratory and heart rates, ataxia, abdominal pain, and lying down have also been noted. These effects are generally seen within 15 minutes of administration and resolve within an hour.

In swine, dinoprost has caused erythema and pruritus, urination, defecation, slight ataxia, hyperpnea, dyspnea, nesting behavior, abdominal muscle spasms, tail movements, increased vocalization and salivation. These effects may last up to 3 hours. At doses of 10 times recommended, vomiting may be seen.

In dogs and cats, dinoprost can cause abdominal pain, emesis, defecation, urination, pupillary dilation followed by constriction, tachycardias, restlessness and anxiety, fever, hypersalivation, dyspnea, and panting. Cats may also exhibit increased vocalization and intense grooming behavior. Severity of effects is generally dose dependent. Defecation can be seen even with very low dosages. Reactions generally appear in 5–120 minutes after administration and may persist for 20–30 minutes. Fatalities have occurred (especially in dogs) after use. Dogs and cats should be monitored for cardiorespiratory effects, especially after receiving higher dosages.

When used as an abortifacient in humans, dinoprost causes nausea, vomiting, or diarrhea in about 50% of patients.

Reproductive/Nursing Safety

Unless being used as an abortifacient or parturition inducer, dinoprost should not be used during pregnancy in all species. In swine, dinoprost should not be administered prior to 3 days of normal predicted farrowing as increased neonatal mortality may result.

Overdosage/Acute Toxicity

Dogs are apparently more sensitive to the toxic effects of dinoprost than other species. The LD_{50} in the bitch has been reported to be 5.13 mg/kg after SC injection, which may be only 5X greater than the recommended dose by some clinicians.

In cattle, swine, and horses, dinoprost's effects when administered in overdose quantities are outlined above in the Adverse Effects section. If clinical signs are severe in any species and require treatment; supportive therapy is recommended.

Drug Interactions

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

- **OTHER OXYTOCIC AGENTS:** Activity may be enhanced by dinoprost. Reduced effect of dinoprost would be expected with concomitant administration of a progestin.

Doses

- **DOGS:**

For treatment of pyometra:

a) Use is restricted to bitches 6 years of age or younger who are not critically ill, do not have significant concurrent illness, do have an open cervix, and an owner who is adamant about saving the animal's reproductive potential. After making definitive diagnosis; use natural prostaglandin F2alpha (*Lutalyse®*): Day 1: 0.1 mg/kg SC once; Day 2: 0.2 mg/kg SC once; Days 3–7: 0.25 mg/kg SC once daily. Use antibiotics (effective against *E. coli*) concurrent with prostaglandin treatment and for 14 days after completion. Reevaluate at 7 and 14 days after treating with prostaglandin. Re-treat at 14 days if purulent discharge persists or fever, increased WBC and fluid filled uterus persist. (Feldman 2000)

b) 0.025–0.25 mg/kg every 12 hours to effect. Initially use lower dosage to determine adverse effects on patient. Dosage depends on adverse effects and clinical condition of animal. For small dogs and cats: Dilute 1 mL (5 mg) of dinoprost injection to 25 mL with sterile water for injection, which will yield a concentration of 0.2 mg/mL (200 micrograms/mL). Adjunctive therapy includes systemic antibiotics (*e.g.*, chloramphenicol, trimethoprim/sulfa, ampicillin) and anterior vaginal douches with 200–500 mL warm 1% tamed iodine (povidone iodine) solution daily during prostaglandin treatment. (Lein 1986)

c) For treatment of cystic endometrial hyperplasia-pyometra: 0.1–0.25 mg/kg once daily until discharge stops, but not for more than 5 days; reexamine in 2 weeks. If discharge has recurred, treat at 0.25–0.5 mg/kg as above. Do not give a third course of therapy. Concurrent antibiotic treatment is necessary. (Shille 1986)

As an abortifacient:

a) After day 25 or 30: SC injections must be given at least twice a day, using a maximum dosage of 80–100 mcg/kg, starting with half the dose for the first day (or first two administrations). Treatment must initially be done under the supervision of a clinician, after which the bitch can be sent home (with owner administration) once side effects have been carefully (monitored) after the first injection. Side effects include: emesis, salivation, defecation, urination and slight tachypnea. Treatment must continue (for 6 days or longer) until verification with ultrasound or palpation. (Romagnoli 2006a)

b) As an adjunctive therapy for the termination of mid-term pregnancy in the bitch: Pregnancy is confirmed with ultrasound and begun no sooner than 30 days after breeding. 1–3 mcg/kg misoprostol given intravaginally once daily concurrently with prostaglandin F2alpha (*Lutalyse®*) at 0.1 mg/kg SC three times daily for 3 days and then 0.2 mg/kg SC three times daily to effect. Monitor efficacy with ultrasound. (Cain 1999)

c) All doses are quoted using the THAM salt (*Lutalyse®*): *During the first half of gestation:* 250 micrograms/kg every 12 hours SC for 4 days, starting at least 5 days after cytologic diestrus. After the eighth injection, draw blood sample for serum progesterone concentration. Examine several weeks post treatment to verify pregnancy termination (failures have been reported). *During second half of gestation:* Verify pregnancy (palpation/ultrasound). Inject 250 micrograms/kg SC every 12 hours until abortion is complete. Treatment efficacy is determined by monitoring the completeness of pregnancy termination. (Root and Johnston 1995)

- **CATS:**

For treatment of pyometra:

a) Initially 0.1 mg/kg SC, then 0.25 mg/kg SC once a day for 5 days. Give bactericidal antibiotics concurrently. Not recommended in animals >8 yrs. old or if severely ill. Closed-cervix pyometra is a relative contraindication. Reevaluate in 2 weeks; retreat for 5 more days if necessary. (Nelson 1988), (Feldman and Nelson 1989)

b) Same as for dogs above (Lein 1986)

As an abortifacient:

a) After day 40 of gestation: 0.5–1 mg/kg SC initially and then 24 hours later. Abortion generally ensues in 8–24 hours. (Woody 1988)

b) 2 mg (total dose) per cat IM once a day beginning at day 33. Side effects include prostration, vomiting and diarrhea. (Romagnoli 2006a)

- **CATTLE:**

For estrus synchronization in beef cattle and non-lactating dairy heifers:

a) 25 mg IM either once or twice at a 10–12 day interval. If using single injection method, breed at usual time relative to estrus. If using dual dose method, breed at either the usual time relative to estrus, or about 80 hours after the second injection. (Package Insert; *Lutalyse®*—Upjohn)

For unobserved (silent) estrus in lactating dairy cattle with a corpus luteum:

a) 25 mg IM. Breed cows as they are detected in estrus. If estrus not detected, breed at 80 hours post injection. If cow returns to estrus, breed at usual time relative to estrus. (Package Insert; *Lutalyse®*—Upjohn)

For pyometra/endometritis:

a) For pyometra: 25 mg IM twice, 8 hours apart; estrus usually ensues in 3–7 days, however evaluation of the uterus using palpation and/or ultrasonography is recommended before these cows are inseminated. For endometritis if a corpus luteum is present: Administration of PGF2a to cows 14 days

apart places 90% of cows between days 5–10 of the estrus cycle, and a conception rate of 45% to the Ovsynch protocol started 12 days after the second injection. (Archibald, Bartolome et al. 2006)

b) For pyometra: 25 mg IM. Uterus begins evacuating within 24 hours of injection (McCormack 1986), (Package Insert; *Lutalyse*®—Upjohn)

As an abortifacient:

a) Between 5–150 days of gestation: 25–30 mg IM. After 150 days of gestation: 25 mg dexamethasone with 25 mg dinoprost (efficacy up to 95%) (Drost 1986)

b) 25 mg IM during the first 100 days of gestation (Package Insert; *Lutalyse*®—Upjohn)

To induce parturition:

a) 25–30 mg IM; delivery will occur in about 72 hours (Drost 1986)

■ **HORSES:**

To induce cyclic activity in animals who are acyclic due to persistent corpus lutea:

a) 5 mg IM; most effective in mares with corpora lutea older than 5 days, and that have progesterone levels >1 ng/mL (4 ng/mL even better) (Rossdale 1987)

For difficult to breed mares secondary to progesterone levels consistent with the presence of a functional corpus luteum:

a) 1 mg per 45 kg body weight IM (Package Insert; *Lutalyse*®—Upjohn)

For controlling time of estrus of estrous cycling mares:

a) 1 mg per 45 kg body weight IM. When treated during diestrus, most mares return to estrus in 2–4 days and ovulate 8–12 days after treatment (Package Insert; *Lutalyse*®—Upjohn)

As an abortifacient:

a) Prior to the 12th day of pregnancy: 5 mg IM. After the 4th month of pregnancy: 1 mg per 45 kg body weight (1 mg per 100 pounds) daily until abortion takes place (Lofstedt 1986)

b) From day 80–300: 2.5 mg q12h; approximately 4 injections required on average to induce abortion (Roberts 1986a)

For estrus synchronization in normally cycling mares:

a) Three methods:

1) *Two injection method:* On day 1 give 5 mg dinoprost and again on day 16. Most (60%) mares will begin estrus 4 days after the second injection and about 90% will show estrous behavior by the 6th day after the second injection. Breed using AI every second day during estrus or inseminate at predetermined times without estrus detection. Alternatively, an IM injection of HCG (2500–3300 Units) can be added on the first or second day (usually day 21) of estrus to hasten ovulation. Breed using AI on days: 20, 22, 24, and 26. This may be of more benefit when used early in the breeding season.

2) *Progestagen/Prostaglandin method:* Give altrenogest (0.44 mg/kg) for 8–12 days PO. On last day of altrenogest therapy (usually day 10) give dinoprost (dose not noted, but suggest using same dose as "1" above). Majority of mares will show estrus 2–5 days after last treatment. Inseminate every 2 days after detection of estrus. Synchronization may be improved by giving 2500 IU of HCG IM on first or second day of estrus or 5–7 days after altrenogest is withdrawn.

3) On day 1, inject 150 mg progesterone and 10 mg estradiol-17beta daily for 10 days. On last day, also give dinoprost (dose not noted, but suggest using same dose as "1" above). Perform AI on alternate days after estrus detection or on days 19, 21, and 23. (Bristol 1987)

■ **SWINE:**

For estrus synchronization (grouping):

a) At 15–55 days of gestation 15 mg dinoprost IM, followed in 12 hours by 10 mg IM. Animals will abort and return to estrus in 4–5 days. Close observation of estrus over several days is needed. (Carson 1986)

As an abortifacient:

a) 5–10 mg IM; abortion occurs in 24–48 hours and estrus occurs 4–5 days later (Drost 1986)

To induce parturition:

a) 10–25 mg IM from 2–6 days before expected parturition; farrowing usually occurs 24–36 hours later (Drost 1986)

■ **SHEEP & GOATS:**

For estrus synchronization in cycling ewes and does:

a) Ewes: Give 8 mg IM on day 5 of estrous cycle and repeat in 11 days. Estrus will begin approximately 2 days after last injection.

b) Does: Give 8 mg IM on day 4 of estrous cycle and repeat in 11 days. Estrus will begin approximately 2 days after last injection. (Carson 1986)

To induce estrous in does (weighing up to 65 kg):

a) 2.5 mg on days 4–17 of estrous cycle

As an abortifacient:

a) Does: 5–10 mg IM throughout entire pregnancy; abortion takes place in 4–5 days.

Ewes (during first two months of pregnancy): 10–15 mg IM; abortion takes place within 72 hours (Drost 1986)

To induce parturition:

a) Does: 2.5–5 mg IM on day 144; parturition occurs in 28–57 hours (Ott 1986a)

b) Does: 2.5–20 mg on days 144–149. Higher dosage (20 mg) yields more predictable interval from injection to delivery (≈32 hours). (Ott 1986b)

For chronic metritis/pyometra:

a) Does: 2.5–5 mg SC with systemic antibiotics (Franklin 1986b)

Monitoring

■ Depending on use, see above. Monitoring for adverse effects is especially important in small animals.

Client Information

■ Dinoprost should be used by individuals familiar with its use and precautions.

■ Pregnant women, asthmatics, or other persons with bronchial diseases should handle this product with extreme caution. Any accidental exposure to skin should be washed off immediately.

Chemistry/Synonyms

The tromethamine (THAM) salt of the naturally occurring prostaglandin F2alpha, dinoprost tromethamine occurs as a white to off-white, very hygroscopic, crystalline powder with a melting point of about 100°C. One gram is soluble in about 5 mL of water. 1.3 micrograms of dinoprost tromethamine is equivalent to 1 micrograms of dinoprost.

Dinoprost and dinoprost tromethamine may also be known as: PGF(2alpha), prostaglandin F(2alpha), idinoprostum trometamoli, PGF(2alpha) THAM, prostaglandin F(2alpha) trometamol, U-14583E, U-14583, *Amtech Prostamate*®, *Lutalyse*®, *Enzaprost*®, *In-Synch*®, *Minprostin F(2)alpha*®, *Prostamate*®, *Prostin*®, *Prostin F2*®, *Prostin F2 Alpha*®, *Prostin F2 Alpha*®, *and Prostine F(2) Alpha*®, *Oriprost*®, *Glandin*®, *Noroprost*®, *Dinolytic*®, and *Prostarmon F*®.

Storage/Stability
Dinoprost for injection should be stored at room temperature (15–30°C) in airtight containers. The human-approved product is recommended to be stored under refrigeration. Dinoprost is considered to be relatively insensitive to heat, light, and alkalis.

Dosage Forms/Regulatory Status
VETERINARY-LABELED PRODUCTS:

Dinoprost Tromethamine for injection, equivalent to 5 mg/mL of dinoprost in 10 mL and 30 mL vials; *Lutalyse® Sterile Solution* (Pharmacia and Upjohn); *Amtech Prostamate®* (IVX); *In-Synch®* (ProLabs); *Prostamate®* (various); (Rx). Approved for use in beef and non-lactating dairy cattle, swine and mares. No preslaughter withdrawal or milk withdrawal is required when used as labeled; no specific tolerance for dinoprost residues has been published. It is not for use in horses intended for food.

HUMAN-LABELED PRODUCTS: None

DIPHENHYDRAMINE HCL

(dye-fen-***hye***-dra-meen) Benadryl®

ANTIHISTAMINE

Prescriber Highlights
- Antihistamine used primarily for its antihistaminic effects, but with various indications (prevention of motion sickness, sedative, antiemetic, etc.)
- Contraindications: Hypersensitive to it or others in class
- Caution: Angle closure glaucoma, GI or urinary obstruction, COPD, hyperthyroidism, seizure disorders, cardiovascular disease or hypertension. May mask clinical signs of ototoxicity.
- Adverse Effects: CNS depression & anticholinergic effects; GI effects (diarrhea, vomiting, anorexia) are less common

Uses/Indications
In veterinary medicine, diphenhydramine is used principally for its antihistaminic effects, but also for other pharmacologic actions. Its sedative effects can be of benefit in treating the agitation (pruritus, etc.) associated with allergic responses. It has also been used for treatment and prevention of motion sickness and as an antiemetic in small animals. It has been suggested for use as adjunctive treatment of aseptic laminitis in cattle and it may be useful as an adjunctive treatment for feline pancreatitis. For other suggested uses, refer to the Dosage section below.

Pharmacology/Actions
Like other antihistamines, diphenhydramine competitively inhibits histamine at H_1 receptors. In addition, it possesses substantial sedative, anticholinergic, antitussive, and antiemetic effects.

Pharmacokinetics
The pharmacokinetics of this agent have apparently not been studied in domestic animals. In humans, diphenhydramine is well absorbed after oral administration, but because of a relatively high first-pass effect, only about 40–60% reaches the systemic circulation.

Following IV administration in rats, diphenhydramine reaches its highest levels in the spleen, lungs and brain. The drug is distributed into milk, but has not been measured quantitatively. In humans, diphenhydramine crosses the placenta and is approximately 80% bound to plasma proteins.

Diphenhydramine is metabolized in the liver and the majority of the drug is excreted as metabolites into the urine. The terminal elimination half-life in adult humans ranges from 2.4–9.3 hours.

Contraindications/Precautions/Warnings
Diphenhydramine is contraindicated in patients who are hypersensitive to it or other antihistamines in its class. Because of their anticholinergic activity, antihistamines should be used with caution in patients with angle closure glaucoma, prostatic hypertrophy, pyloroduodenal or bladder neck obstruction, and COPD if mucosal secretions are a problem. Additionally, they should be used with caution in patients with hyperthyroidism, cardiovascular disease or hypertension.

Adverse Effects
The most commonly seen adverse effects are CNS depression (lethargy, somnolence), and anticholinergic effects (dry mouth, urinary retention). The sedative effects of antihistamines may diminish with time. GI effects (diarrhea, vomiting, anorexia) are a possibility.

The sedative effects of antihistamines may adversely affect the performance of working dogs.

Diphenhydramine may cause paradoxical excitement in cats. The liquid formulation is very distasteful.

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: ***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.*)

Diphenhydramine is excreted milk. Use with caution, particularly in neonates.

Overdosage/Acute Toxicity
Overdosage can cause CNS stimulation (excitement to seizures) or depression (lethargy to coma), anticholinergic effects, respiratory depression and death. Treatment consists of emptying the gut after oral ingestion using standard protocols. Induce emesis if the patient is alert and CNS status is stable. Administration of a saline cathartic and/or activated charcoal may be given after emesis or gastric lavage. Treatment of other clinical signs should be performed using symptomatic and supportive therapies. Phenytoin (IV) is recommended in the treatment of seizures caused by antihistamine overdose in humans; barbiturates and diazepam should be avoided.