Monitoring
- Periodic quantitative hepatic copper levels

Client Information
- While it is preferable to give on an empty stomach, if the drug causes vomiting or lack of appetite give with a small amount of food

Chemistry/Synonyms
An oral copper chelator, trientine HCl occurs as a white to pale yellow crystalline powder. It is hygroscopic and freely soluble in water.

Trientine HCl may also be known as: MK-0681, 2,2,2-tetramine, trien hydrochloride, triethylenetetramine dihydrochloride, trientine hydrochloride or *Syprine*®.

Storage/Stability
Store trientine capsules in the refrigerator (2–8°C) in tightly closed containers.

Dosage Forms/Regulatory Status
VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Trientine HCl Capsules: 250 mg; *Syprine*® (Merck); (Rx)

TRILOSTANE

(***trye***-loe-stane) Vetoryl®

ADRENAL STEROID SYNTHESIS INHIBITOR

Prescriber Highlights
- Competitive inhibitor of 3-beta hydroxysteroid dehydrogenase thereby reducing synthesis of cortisol, aldosterone, & adrenal androgens
- May be useful in dogs for treatment of pituitary-dependent hyperadrenocorticism, adrenal dependent hyperadrenocorticism, Alopecia X in Pomeranians & Alaskan malamutes; in cats for treatment of feline pituitary dependent hyperadrenocorticism, & in horses for equine hyperadrenocorticism (HAC)
- In USA, must presently be imported
- Potential adverse effects in dogs include lethargy, inappetence, vomiting, electrolyte abnormalities, & diarrhea
- Rare case reports of hypoadrenocorticism & death
- Expense of treatment may be an issue

Uses/Indications
Trilostane may be useful for treating pituitary-dependent hyperadrenocorticism or adrenal dependent hyperadrenocorticism in dogs, feline pituitary-dependent hyperadrenocorticism, and equine hyperadrenocorticism (HAC). It may also be useful in treating Pomeranians with Alopecia X and Alaskan malamutes with adult-onset alopecia.

Pharmacology/Actions
Trilostane is a competitive inhibitor of 3-beta hydroxysteroid dehydrogenase thereby reducing synthesis of cortisol, aldosterone, and adrenal androgens. Inhibition is reversible and apparently dose dependent.

Pharmacokinetics
In dogs, orally administered trilostane is rapidly, but erratically absorbed with peak levels occurring between 1.5–2 hours post dose. It is unknown whether the presence of food in the gut significantly alters absorption characteristics. After 18 hours, the drug reportedly returns to baseline levels. Effects on cortisol production apparently last for no more than 20 hours, and more likely wane within 10 hours of dosing. Trilostane is metabolized in the liver to several metabolites including ketotrilostane, which is active.

Contraindications/Precautions/Warnings
Trilostane is contraindicated in animals hypersensitive to it. It should be used with caution in patients with renal or hepatic impairment.

Adverse Effects
Trilostane appears to be relatively well tolerated in dogs. Lethargy, mild electrolyte abnormalities and inappetence are commonly noted during the first few days of therapy secondary to steroid withdrawal. Vomiting and diarrhea may also be seen. Withholding the drug for a few days and then giving it every other day for a week may alleviate lethargy and vomiting. Rarely, acute death or development of hypoadrencorticism (including adrenal necrosis) occurring in dogs after receiving trilostane have been anecdotally reported.

In one study of trilostane given to 20 horses with equine Cushing's (McGowan and Neiger 2003), no adverse effects were noted.

Reproductive/Nursing Safety
Because trilostane can significantly reduce the synthesis of progesterone *in vivo*, it should not be used in pregnancy. Trilostane reportedly (not confirmed) is classified by the FDA as a category ***X*** drug (*Contraindicated in pregnancy*).

Information on trilostane levels in maternal milk were not located; use with caution in lactating animals.

Overdosage/Acute Toxicity
Specific information on trilostane acute toxicity was not located. One source states that trilostane overdoses would be unlikely to threaten life and no clinical signs would be expected. However, blood pressure, hydration status, and electrolyte balance should be monitored. If the animal is stressed, consider giving exogenous corticosteroids short-term. Because the drug's effects are relatively short lived, monitoring of patients without complications should only be required for a few days post ingestion.

Drug Interactions
The following drug interactions have either been reported or are theoretical in humans or animals receiving trilostane and may be of significance in veterinary patients:
- **ACE INHIBITORS** (*e.g.,* **benazepril, enalapril**): Could increase risk for hyperkalemia
- **AMINOGLUTETHIMIDE:** May potentiate the effects of trilostane and lead to hypoadrenocorticism
- **KETOCONAZOLE:** May potentiate the effects of trilostane and lead to hypoadrenocorticism
- **MITOTANE:** May potentiate the effects of trilostane and lead to hypoadrenocorticism
- **POTASSIUM-SPARING DIURETICS** (*e.g.,* **spironolactone**): Could increase risk for hyperkalemia
- **POTASSIUM-SUPPLEMENTS; HIGH POTASSIUM FOODS**: Could increase risk for hyperkalemia

Laboratory Considerations

- No specific laboratory interactions or considerations were located.

Doses

- **DOGS:**

For treatment of canine hyperadrenocorticism (HAC):

a) For treatment of canine hyperadrenocorticism (HAC) whether due to adrenal tumor or PDH: Initial therapy at 2–10 mg/kg PO once daily. Adjust dosage per monitoring parameters below. Doses of up to 50 mg/kg/day divided twice daily have been given without untoward side effects. Give with food. Some dogs require twice daily administration.

ACTH stimulation test done at 10–14 days, 30 days and 90 days after starting therapy. ACTH stimulation tests should be performed 4–6 hours post-trilostane dose. Interpret ACTH test in light of physical exam. If ACTH Stim results are <20 nmol/L (0.72 mcg/dl), then the drug is discontinued for 48–72 hours and then re-started at a lower dosage. If ACTH Stim results are >200 nmol/L (7.2 mcg/dl), then the dose is increased. If the ACTH Stim results are between these two values and the dog is clinically well-controlled, then no change. If between these two results and the patient appears not to be clinically well-controlled, then the drug may need to be given twice daily. Once the dog is stable, repeat ACTH Stim test every 3–6 months. (Neiger 2004)

b) Author's (Feldman) experience is that trilostane is not more effective or safer than mitotane and that trilostane is less predictable (under dose, over dose, resolution of signs, or the need for dosing more than once per day) than mitotane.

If using trilostane current recommendation is: Initiate at 1 mg/kg PO once daily and continue for about one week until a veterinary recheck can occur. Have owners collect a small urine sample from their dog before leaving home the morning of the scheduled recheck prior to trilostane administration. Trilostane should then be given and the dog should be seen by veterinarian 2 to 3 hours later. The goal of therapy is an owner who is completely pleased with the response. The urine should be checked, at a minimum, for specific gravity, glucose and urine cortisol:creatinine ratio (UCCR). An ACTH stimulation test should be started at the time that the dog is seen (about 2 to 3 hours after trilostane dose). The UCCR result should be within the reference interval and the post-ACTH serum cortisol concentration should be between 1.5 and 5.5 mcg/dL. If the serum cortisol concentration is within that goal and the UCCR is abnormal, the medication should be given twice daily. If the serum cortisol concentration is too high, the trilostane dose should be increased and if the serum cortisol concentration is too low, the dose should be decreased. This approach should be utilized at each recheck until the dog is doing well. (Feldman 2007)

For treatment of Alopecia X:

a) In Alaskan Malamutes: 3–3.6 mg/kg PO twice a day for 4–6 months. Three dogs treated; no adverse effects reported. (Leone, Vercelli et al. 2005)

b) In Miniature poodles and Pomeranians: Average dose was 10.85 mg/kg per day given either once a day or divided twice a day for 4–8 weeks. (Cerundolo, Lloyd et al. 2004)

- **CATS:**

a) For treatment of feline hyperadrenocorticism: 7 mg/kg/day divided and given twice daily. Doses of up to 60 mg per cat per day have been used in a small number of cats with PDH. (Greco 2007a)

- **HORSES:**

a) For treatment of equine Cushing's syndrome: 0.4–1 mg/kg (total dose 120–240 mg) PO once daily. (McGowan and Neiger 2003)

Monitoring

- Clinical effects
- Adverse effects
- Serum electrolytes
- Urinalysis including specific gravity, glucose and urine cortisol:creatinine ratio (UCCR)
- ACTH stimulation tests (see doses for recommendations)

Client Information

- Keep out of reach of children and pets
- Wear gloves or wash hands thoroughly after handling
- Clients should report any adverse effects to the veterinarian
- Give the drug with food, unless otherwise directed by veterinarian
- Clients should understand that trilostane is a treatment for the condition and not a cure

Chemistry/Synonyms

A synthetic steroid analog, trilostane has a molecular weight of 329.4 and its chemical name is 4-alpha, 5-alpha-Epoxy-17-beta-hydroxy-3-oxoandrostane-2-alpha-carbonitrile. It reportedly is relatively insoluble in water.

Trilostane may also be known as: WIN 24540, *Vetoryl®, Desopan®*, *Modrastane®* or *Modrenal®*.

Storage/Stability/Compatibility

Commercially available trilostane capsules should be stored at room temperature in tight, light-resistant containers.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None in the USA.

In the UK, Trilostane Oral Capsules 60 mg, 120 mg are available. Trade name is *Vetoryl®* (Arnolds Veterinary Products, Cartmel Drive, Harlescott, Shrewsbury, Shropshire SY1 3TB, U.K.; FAX Number: +44 0174346211). *Vetoryl®* can be legally imported into the USA by obtaining prior approval from the FDA. See the appendix for stepwise instructions.

One source that has been recommended for obtaining trilostane after obtaining FDA approval is: www.mastersmarketing.com (Mealey 2007)

HUMAN-LABELED PRODUCTS:

Modrastane® is reportedly still an approved human drug, but was withdrawn from the market in the USA in 1994.

TRIMEPRAZINE TARTRATE WITH PREDNISOLONE

(trye-***mep***-ra-zeen) Temaril-P®

PHENOTHIAZINE ANTIHISTAMINE & CORTICOSTEROID

Prescriber Highlights

- Combination phenothiazine antihistamine & corticosteroid used for pruritus & potentially as an antitussive
- Relatively Contraindicated: Systemic fungal infections, hypovolemia, or shock & in patients with tetanus or strychnine intoxication. Caution: Hepatic dysfunction, cardiac disease, active bacterial or viral infections, peptic ulcer, acute psychoses, corneal ulcer, Cushingoid syndrome, diabetes, osteoporosis, chronic psychotic reactions, predisposition to thrombophlebitis, hypertension, CHF, renal insufficiency, general debilitation, very young animals
- Goal is to use as much as is required & as little as possible for as short an amount of time as possible
- Primary adverse effects: Sedation, may cause significant hypotension, cardiac rate abnormalities, hypo- or hyperthermia, "Cushingoid" effects with sustained use
- Many potential drug & lab interactions

Uses/Indications

Trimeprazine with prednisolone is used for the treatment of pruritic conditions, especially if induced by allergic conditions. Many dermatologists believe that when prednisolone is combined with trimeprazine (*Temaril-P*®), less prednisolone is required to control pruritus. The manufacturer suggests the drug is for use in dogs either for pruritic conditions or as an antitussive.

Pharmacology/Actions

Trimeprazine has antihistaminic, sedative, antitussive, and antipruritic qualities. The veterinary-approved product also has prednisolone in its formulation that provides additional antiinflammatory effects.

Pharmacokinetics

The pharmacokinetics of trimeprazine have apparently not been studied.

Contraindications/Precautions/Warnings

The contraindications and precautions of this product follow those of the other phenothiazines and antihistaminic agents. For more information, it is suggested to review the acepromazine and chlorpheniramine monographs.

Adverse Effects

For trimeprazine, possible adverse reactions include: sedation, depression, hypotension and extrapyramidal reactions (rigidity, tremors, weakness, restlessness, etc.).

Additional adverse effects, if using the product containing steroids include: elevated liver enzymes, weight loss, polyuria/polydipsia, vomiting, and diarrhea. If used chronically, therapy must be withdrawn gradually and Cushing's syndrome may develop.

The manufacturer of the veterinary combination product (*Temaril*®*-P*) includes the following adverse effects in its package insert: sodium retention and potassium loss, negative nitrogen balance, suppressed adrenocortical function, delayed wound healing, osteoporosis, possible increased susceptibility to and/or exacerbation of bacterial infections, sedation, protruding nictitating membrane, blood dyscrasias. In addition, intensification and prolongation of the action of sedatives, analgesics or anesthetics can be noted and potentiation of organophosphate toxicity and of procaine HCl activity.

Reproductive/Nursing Safety

The manufacturer of the veterinary combination product (*Temaril*®*-P*) warns that corticosteroids can induce the first stages of parturition if administered during the last trimester of pregnancy.

Overdosage/Acute Toxicity

Acute overdosage should be handled as per the acepromazine monograph found at the beginning of the book.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving promethazine (a related phenothiazine antihistamine) or prednisolone and may be of significance in veterinary patients:

- **ACE INHIBITORS:** Phenothiazines may increase effects
- **AMPHOTERICIN B:** When administered concomitantly with glucocorticoids may cause hypokalemia
- **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
- **ANTICHOLINESTERASE AGENTS** (*e.g.*, **pyridostigmine, neostigmine,** etc.): In patients with myasthenia gravis, concomitant glucocorticoid with these agents may lead to profound muscle weakness. If possible, discontinue anticholinesterase medication at least 24 hours prior to corticosteroid administration.
- **ASPIRIN** (**salicylates**): Glucocorticoids may reduce salicylate blood levels
- **CISAPRIDE:** Increased risk for cardiac arrhythmias when used with phenothiazines
- **CNS DEPRESSANT AGENTS** (**barbiturates, narcotics, anesthetics**, etc.): May cause additive CNS depression if used with phenothiazines
- **CYCLOPHOSPHAMIDE:** Glucocorticoids may also inhibit the hepatic metabolism of cyclophosphamide; dosage adjustments may be required.
- **CYCLOSPORINE:** Concomitant administration of may increase the blood levels of each, by mutually inhibiting the hepatic metabolism of each other; clinical significance of this interaction is not clear
- **DIGOXIN:** Secondary to hypokalemia, increased risk for arrhythmias
- **DIURETICS, POTASSIUM-DEPLETING** (**furosemide, thiazides**): When administered concomitantly with glucocorticoids may cause hypokalemia
- **EPHEDRINE:** May increase metabolism
- **ESTROGENS:** The effects of hydrocortisone, and possibly other glucocorticoids, may be potentiated by concomitant administration with estrogens
- **INSULIN:** Requirements may increase in patients receiving glucocorticoids
- **KETOCONAZOLE:** May decrease metabolism