creted into the urine. In humans, the serum half life of misoprostol is about 30 minutes and its duration of pharmacological effect is about 3-6 hours.

Contraindications/Precautions/Reproductive Safety - Misoprostol is contraindicated during pregnancy due to its abortifacient activity. It is not recommended to be used in nursing mothers as it potentially could cause significant diarrhea in the nursing offspring.

It should be used in patients with the following conditions only when its potential benefits outweigh the risks: Sensitivity to prostaglandins or prostaglandin analogs; patients with cerebral or coronary vascular disease (although not reported with misoprostol, some prostaglandins and prostaglandin analogs have precipitated seizures in epileptic human patients, and have caused hypotension which may adversely affect these patients).

Adverse Effects/Warnings - The most prevalent adverse effect seen with misoprostol is GI distress, usually manifested by diarrhea, abdominal pain, vomiting and flatulence. Adverse effects are often transient and resolve over several days or may be minimized by dosage adjustment or giving doses with food. Potentially, uterine contractions and vaginal bleeding could occur in female dogs.

Overdosage/Acute Toxicity - There is limited information available. Overdoses in laboratory animals have produced diarrhea, GI lesions, emesis, tremors, focal cardiac, hepatic or renal tubular necrosis, seizures and hypotension. Overdoses should be treated seriously and standard gut emptying techniques employed when applicable. Resultant toxicity should be treated symptomatically and supportively.

Drug Interactions - **Magnesium-containing antacids** may aggravate misoprostol-induced diarrhea. If an antacid is required and aluminum-only antacid may be a better choice. **Antacids and food** do reduce the rate of absorption and may reduce the systemic availability, but probably do not affect therapeutic efficacy.

Doses -

Dogs:

For the prevention and treatment of GI ulcers:

a) 1 - 3 µg/kg PO q6-8h (Davenport 1992)
b) 2 - 5 µg/kg PO q8-12h (Papich 1992)
c) 3 - 5 µg/kg PO q6h (Johnson, Sherding et al. 1994)

Monitoring Parameters - Efficacy and adverse effects

Client Information - Caution pregnant women to handle the drug with caution. If diarrhea or other GI adverse effects become severe or persist, reduce dose or give with food or aluminum antacids to alleviate. Severe diarrhoeas may require supportive therapy.

Dosage Forms/Preparations/FDA Approval Status/Withholding Times -

Veterinary-Labeled Products: None

Human-Approved Products:

Misoprostol Oral Tablets 100 µg, 200 µg; *Cytotec*® (Searle); (Rx)

MITOTANE
O, P' - DDD

Chemistry - Mitotane, also commonly known in veterinary medicine as *o,p'*-DDD, is structurally related to the infamous insecticide, chlorophenothane (DDT). It occurs as a white, crystalline powder with a slightly aromatic odor. It is practically insoluble in water and soluble in alcohol.

Storage/Stability/Compatibility - Mitotane tablets should be stored at room temperature (15-30°C), in tight, light resistant containers.

Pharmacology - While mitotane is considered to be an adrenal cytotoxic agent, it apparently can also inhibit adrenocortical function without causing cell destruction. The exact mechanisms of action for these effects are not clearly understood.

In dogs with pituitary-dependent hyperadrenocorticism (PDH), mitotane has been demonstrated to cause severe, progressive necrosis of the zona fasiculata and zona reticularis. These effects occur quite rapidly (within days of starting therapy). It has been stated that mitotane spares the zona glomerulosa and therefore aldosterone synthesis is unaffected. This is only partially true, as the zona glomerulosa may also be affected by mitotane therapy, but it is uncommon for clinically significant effects on aldosterone production to be noted with therapy.

Uses/Indications - In veterinary medicine, mitotane is used primarily for the medical treatment of pituitary-dependent hyperadrenocorticism (PDH), principally in the dog. It has also been used for the palliative treatment of adrenal carcinoma in humans and dogs.

Pharmacokinetics - No pharmacokinetic data was located on this drug for veterinary species. In humans, approximately 40% of an oral dose of mitotane is absorbed after dosing, with peak serum levels occuring about 3-5 hours after a single dose. Distribution of the drug occurs to virtually all tissues in the body. The drug is stored in the fat and does not accumulate in the adrenal glands. A small amount may enter the CSF. It is unknown if the drug crosses the placenta or is distributed into milk.

Mitotane has a very long plasma half-life in humans, with values ranging from 18-159 days being reported. The drug is metabolized in the liver and is excreted as metabolites in the urine and bile. Approximately 15% of an oral dose is excreted in the bile, and 10% in the urine within 24 hours of dosing.

Contraindications/Precautions - Mitotane is contraindicated in patients known to be hypersensitive to it. As it is unknown whether mitotane crosses the placenta, it should be used in pregnant bitches cautiously. As it is also unknown if the drug enters into milk, it's suggested that puppies be given milk replacer after receiving colostrum if the mother is receiving mitotane.

Patients with concurrent diabetes mellitus may have rapidly changing insulin requirements during the initial treatment period. These animals should be closely monitored until they are clinically stable.

Dogs with preexisting renal or hepatic disease should receive the drug with caution and with more intense monitoring.

Some clinicians recommend giving prednisolone at 0.2 mg/kg/day during the initial treatment period (0.4 mg/kg/day to diabetic dogs) to reduce the potential for side effects from acute endogenous steroid withdrawal. Other clinicians have argued that routinely administering steroids masks the clinical markers that signify when the endpoint of therapy has been reached and must be withdrawn 2-3 days before ACTH stimulation tests can be done. Since in adequately observed patients, adverse effects requiring glucocorticoid therapy may only be necessary in 5% of patients, the benefits of routine glucocorticoid administration may not be warranted.

Adverse Effects/Warnings - Most common adverse effects seen with initial therapy in dogs include lethargy, ataxia, weakness, anorexia, vomiting, and/or diarrhea. Adverse effects are commonly associated with plasma cortisol levels of less than 1 µg/dl or a too rapid decrease of plasma cortisol levels into the normal range. Adverse effects may also be more commonly seen in dogs weighing less than 5 kg, which may be due to the inability to accurately dose. The incidence of one or more of these effects is approximately 25% and they are usually mild. If adverse effects are noted, it is recommended to temporarily halt mitotane therapy and supplement with glucocorticoids. Owners should be provided with a small supply of predniso(lo)ne tablets to initiate treatment. Should the symptoms persist 3 hours after steroids are supplemented, consider other medical problems.

Liver changes (congestion, centrolobular atrophy, and moderate to severe fatty degeneration) have been noted in dogs given mitotane. Although not commonly associated with clinical symptomatology, these effects may be more pronounced with long-term therapy or in dogs with preexisting liver disease.

In perhaps 5% of dogs treated, long-term glucocorticoid and sometimes mineralocorticoid replacement therapy may be required. All dogs receiving mitotane therapy should receive additional glucocorticoid supplementation if undergoing a stress (*e.g.*, surgery, trauma, acute illness).

Overdosage - No specific recommendations were located regarding overdoses of this medication. Because of the drug's toxicity and long half-life, emptying the stomach and administering charcoal and a cathartic should be considered after a recent ingestion. It is recommended that the patient be closely monitored and given glucocorticoids if necessary.

Drug Interactions - Mitotane may induce hepatic microsomal enzymes and, therefore, could increase the metabolism of certain drugs (*e.g.*, **barbiturates, warfarin**).

If mitotane is used concomitantly with drugs that cause **CNS depression**, additive depressant effects may be seen.

Diabetic dogs receiving **insulin**, may have their insulin requirements decreased when mitotane therapy is instituted.

In dogs, **spironolactone** has been demonstrated to block the action of mitotane. It is recommended to use an alternate diuretic if possible.

Drug/Laboratory Interactions - Mitotane will bind competitively to thyroxine-binding globulin and decreases the amount of serum protein-bound iodine. Serum thyroxine concentrations may be unchanged or

slightly decreased, but free tayroxine values remain in the normal range. Mitotane does not affect the results of the resin triiodothyronine uptake test.

Mitotane can reduce the amounts measurable 17-OHCS in the urine, which may or may not reflect a decrease in serum cortisol levels or adrenal secretion.

Doses -

Dogs:

For medical treatment of pituitary-dependent hyperadrenocorticism (bilateral adrenal hyperplasia): **Note:** The information provided below (in "a") is a synopsis of the author's treatment protocol. It is strongly recommended to refer to the original reference and read the entire discussion before instituting therapy for the first time.

a) Initiate therapy at home (preferably on a Saturday): 50 mg/kg divided twice a day PO. Do not give glucocorticoids, but owner should have a small supply of prednisolone. Give until one of the following occurs: Polydipsic dogs consume less than 60 ml/kg/day of water; dogs' with excellent appetite takes 10-30 minutes longer than before mitotane therapy to consume meals (feed two small meals twice daily); dog vomits, is listless, or has diarrhea. Beginning on 3rd day of therapy, contact owner daily to monitor the situation and encourage. If dog develops GI upset 3-4 days after starting therapy; evaluate and either temporarily halt therapy or divide dosage further.

After 8-9 days after therapy initiated, the dog should be evaluated and history and physical repeated, ACTH response test, BUN, serum sodium and potassium redone. If the dog has responded clinically, stop mitotane until ACTH response test can be evaluated. If the response test yields normal or high cortisol values, mitotane is continued (generally for 3-7 days). Repeat ACTH response test every 7-10 days until a low post-ACTH cortisol level is obtained. Most dogs respond during the first 7-10 days and nearly all respond by the 16th day of therapy.

Maintenance therapy: Dogs who have responded to mitotane within 10 days of initiation receive 25 mg/kg every 7 days. Recheck ACTH response every 1-3 months. Those taking longer than 10 days to respond, receive 50 mg/kg weekly. If ACTH-stimulated cortisol levels begin to increase, mitotane dosage should be increased. Dogs with recurrent signs and symptoms of PDH or post ACTH cortisol values of > 5 µg/dl, should undergo daily therapy as outlined above. These animals should also be evaluated for other conditions (*e.g.*, renal disease, diabetes mellitus). Should anorexia and listlessness be seen with low plasma cortisol levels, reduce dosage. (Feldman 1989)

For palliative medical treatment of adrenal carcinomas or medical treatment of adrenal adenomas:

a) Initially, 50 - 75 mg/kg PO in daily divided doses for 10-14 days. May supplement with prednisolone at 0.2 mg/kg/day. Stop therapy and evaluate dog if adverse effects occur. After initial therapy run ACTH-stimulation test (do not give prednisolone the morning of the test). If basal or post-ACTH serum cortisol values are decreased, but still above the therapeutic end-point (<1 µg/dl), repeat therapy for an additional 7-14 days and repeat testing.

If post-ACTH serum cortisol values remain greatly elevated or unchanged, increase mitotane to 100 mg/kg/day and repeat ACTH-stimulation test at 7-14 day intervals. If continues to remain greatly elevated, increase dosage by 50 mg/kg/day every 7-14 days until response occurs or drug intolerance ensues. Adjust dosage as necessary as patient tolerates or ACTH-responsive dictates.

Once undetectable or low-normal post-ACTH cortisol levels are attained, continue mitotane at 100 - 200 mg/kg/week in divided doses with glucocorticoid supplementation (prednisolone 0.2 mg/kg/day). Repeat ACTH-stimulation test in 1-2 months, continue at present dose if cortisols remain below 1 µg/dl. Should cortisols increase to 1 - 4 µg/dl, increase maintenance dose by 50%. If basal or post-ACTH cortisols go above 4 µg/dl, restart daily treatment (50 - 100 mg/kg/day) as outlined above. Once patient is stabilized, repeat ACTH-stimulation tests at 3-6 month intervals. (Kintzer and Peterson 1989)

Monitoring Parameters -

Initially and *prn* (see doses above):

1) Physical exam and history (including water and food consumption, weight)
2) BUN, CBC, Liver enzymes, Blood glucose, ACTH response test, serum electrolytes (Na^+/K^+)

Client Information - Clients must be clearly instructed in the adverse effects of the drug and the symptoms of acute hypoadrenocorticism. Because of the potential severe toxicity associated with this agent,