Storage/Stability
Fludrocortisone acetate tablets should be stored at room temperature (15–30°C) in well-closed containers; avoid excessive heat. The drug is relatively stable in light and air.

Dosage Forms/Regulatory Status
VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Fludrocortisone Acetate Tablets: 0.1 mg; *Florinef® Acetate* (Monarch); generic; (Rx)

FLUMAZENIL

(floo-*maz*-eh-nill) Romazicon®

BENZODIAZEPINE ANTAGONIST

Prescriber Highlights

- Benzodiazepine antagonist to reverse either OD's or therapeutic effects
- Contraindications: Known hypersensitivity, when benzodiazepines are treating life-threatening conditions (*e.g.*, status epilepticus, increased CSF pressure), during tricyclic antidepressant OD treatment
- Use extreme caution in mixed overdoses
- Adverse Effects: Potentially injection site reactions, vomiting, cutaneous vasodilatation, vertigo, ataxia, & blurred vision; seizures have been reported in humans
- Potentially teratogenic at high dosages

Uses/Indications
Flumazenil may be useful for the reversal of benzodiazepine effects after either therapeutic use or overdoses. Flumazenil may be of benefit in the treatment of encephalopathy in patients with severe hepatic failure.

Pharmacology/Actions
Flumazenil is a competitive blocker of benzodiazepines at benzodiazepine receptors in the CNS. It antagonizes the sedative and amnestic qualities of benzodiazepines.

Pharmacokinetics
Flumazenil is administered by rapid IV injection. Therapeutic effect may occur within 1–2 minutes of administration. It is rapidly distributed and metabolized in the liver. In humans, the average half-life is about one hour.

Contraindications/Precautions/Warnings
Flumazenil is contraindicated in patients hypersensitive to it or other benzodiazepines or in patients with where benzodiazepines are being used to treat a potentially life-threatening condition (*e.g.*, status epilepticus, increased CSF pressure). It should not be used in patients with a serious tricyclic antidepressant overdose. Flumazenil should not be used, or used with extreme caution, in patients with mixed overdoses where benzodiazepine reversal may lead to seizures or other complications.

Flumazenil does not alter benzodiazepine pharmacokinetics. Effects of long-acting benzodiazepines may recur after flumazenil's effects subside.

Adverse Effects
In some human patients, flumazenil use has been associated with seizures. These patients usually have a long history of benzodiazepine use or are showing signs of serious tricyclic antidepressant toxicity. Adverse effects reported in humans include injection site reactions, vomiting, cutaneous vasodilatation, vertigo, ataxia and blurred vision. Deaths have been associated with its use in humans having serious underlying diseases.

Overdosage/Acute Toxicity
Large IV overdoses have rarely caused symptoms in otherwise healthy humans. Seizures, if precipitated, have been treated with barbiturates, benzodiazepines and phenytoin, usually with prompt responses.

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

- **CYCLIC** (tri-, tetra-) **ANTIDEPRESSANTS** (*e.g.*, **clomipramine, amitriptyline**, etc.): Increased risk for seizures; use contraindicated
- **NEUROMUSCULAR BLOCKING AGENTS**: Not recommended to use flumazenil until neuromuscular blockade has been fully reversed

Doses
- **DOGS & CATS:**

  As an antagonist for benzodiazepines:
  a) Dogs: 0.01 mg/kg IV (Bunch 2003)
  b) Dogs/Cats: 0.01 mg/kg IV; may need to be repeated as half-life is only about an hour. May also be administered intratracheally in an emergency. (Wismer 2004)

  For adjunctive therapy to improve neurologic function in dogs with severe hepatic encephalopathy:
  a) 0.02 mg/kg IV (one time) (Bunch 2003)
  b) 0.02 mg/kg IV; if animal responds, safe to use repeatedly (Michel 2003)

Monitoring
- Efficacy
- Monitor for seizures in susceptible patients

Client Information
- Flumazenil should only be used in a controlled environment by clinically experienced professionals.

Chemistry/Synonyms
A benzodiazepine antagonist, flumazenil is a 1,4-imidazobenzodiazepine derivative.

Flumazenil may also be known as: flumazenilum, flumazepil, Ro-15-1788, Ro-15-1788/000, *Anexate®*, *Fadaflumaz®*, *Flumage®*, *Flumanovag®*, *Flumazen®*, *Fluxifarm®*, *Lanexat®* and *Romazicon®*.

Storage/Stability/Compatibility
Flumazenil is physically **compatible** with lactated Ringer's, D_5W, or normal saline solutions. Once drawn into a syringe or mixed with the above solutions, discard after 24 hours.

Dosage Forms/Regulatory Status
VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Flumazenil Injection: 0.1 mg/mL in 5 mL and 10 mL vials; *Romazicon®* (Hoffman-LaRoche); generic; (Rx)

FLUMETHASONE

(floo-*meth*-a-sone) Flucort®

GLUCOCORTICOID

Prescriber Highlights

- Injectable & oral glucocorticoid (oral may not be available commercially in USA)
- Long-acting; 15–30X more potent than hydrocortisone; no appreciable mineralocorticoid activity
- Therapy 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 are "Cushingoid" in nature with sustained use
- Many potential drug & lab interactions

Uses/Indications

Flumethasone injection (*Flucort*®) is labeled in horses as indicated for: **1)** Musculoskeletal conditions due to inflammation, where permanent structural changes do not exist, such as bursitis, carpitis, osselets and myositis. Following therapy an appropriate period of rest should be instituted to allow a more normal return to function of the affected part. **2)** In allergic states such as hives, urticaria and insect bites.

Flumethasone injection (*Flucort*®) is labeled in dogs as indicated for: **1)** Musculoskeletal conditions due to inflammation of muscles or joints and accessory structures, where permanent structural changes do not exist, such as arthritis, osteoarthritis, the disc syndrome and myositis. In septic arthritis appropriate antibacterial therapy should be concurrently administered. **2)** In certain acute and chronic dermatoses of varying etiology to help control the pruritus, irritation and inflammation associated with these conditions. The drug has proven useful in otitis externa in conjunction with topical medication for similar reasons. **3)** In allergic states such as hives, urticaria and insect bites. **4)** Shock and shock-like states, by intravenous administration.

Flumethasone injection (*Flucort*®) is labeled in cats as indicated for certain acute and chronic dermatoses of varying etiology to help control the pruritus, irritation and inflammation associated with these conditions.

Glucocorticoids have been used in an attempt to treat practically every malady that afflicts man or animal, but there are three broad uses and dosage ranges for use of these agents. **1)** Replacement of glucocorticoid activity in patients with adrenal insufficiency, **2)** as an antiinflammatory agent, and **3)** as an immunosuppressive. Among some of the uses for glucocorticoids include treatment of: endocrine conditions (*e.g.*, adrenal insufficiency), rheumatic diseases (*e.g.*, rheumatoid arthritis), collagen diseases (*e.g.*, systemic lupus), allergic states, respiratory diseases (*e.g.*, asthma), dermatologic diseases (*e.g.*, pemphigus, allergic dermatoses), hematologic disorders (*e.g.*, thrombocytopenias, autoimmune hemolytic anemias), neoplasias, nervous system disorders (increased CSF pressure), GI diseases (*e.g.*, ulcerative colitis exacerbations), and renal diseases (*e.g.*, nephrotic syndrome). Some glucocorticoids are used topically in the eye and skin for various conditions or are injected intra-articularly or intra-lesionally. The above listing is certainly not complete.

Pharmacology/Actions

Glucocorticoids have effects on virtually every cell type and system in mammals. An overview of the effects of these agents follows:

Cardiovascular System: Glucocorticoids can reduce capillary permeability and enhance vasoconstriction. A relatively clinically insignificant positive inotropic effect can occur after glucocorticoid administration. Increased blood pressure can result from both the drugs' vasoconstrictive properties and increased blood volume that may be produced.

Cells: Glucocorticoids inhibit fibroblast proliferation, macrophage response to migration inhibiting factor, sensitization of lymphocytes and the cellular response to mediators of inflammation. Glucocorticoids stabilize lysosomal membranes.

CNS/Autonomic Nervous System: Glucocorticoids can lower seizure threshold, alter mood and behavior, diminish the response to pyrogens, stimulate appetite and maintain alpha rhythm. Glucocorticoids are necessary for normal adrenergic receptor sensitivity.

Endocrine System: When animals are not stressed, glucocorticoids will suppress the release of ACTH from the anterior pituitary, thereby reducing or preventing the release of endogenous corticosteroids. Stress factors (*e.g.*, renal disease, liver disease, diabetes) may sometimes nullify the suppressing aspects of exogenously administered steroids. Release of thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), prolactin, and luteinizing hormone (LH) may all be reduced when glucocorticoids are administered at pharmacological doses. Conversion of thyroxine (T_4) to triiodothyronine (T_3) may be reduced by glucocorticoids; and plasma levels of parathyroid hormone increased. Glucocorticoids may inhibit osteoblast function. Vasopressin (ADH) activity is reduced at the renal tubules and diuresis may occur. Glucocorticoids inhibit insulin binding to insulin-receptors and the post-receptor effects of insulin.

Hematopoietic System: Glucocorticoids can increase the numbers of circulating platelets, neutrophils and red blood cells, but platelet aggregation is inhibited. Decreased amounts of lymphocytes (peripheral), monocytes and eosinophils are seen as glucocorticoids can sequester these cells into the lungs and spleen and prompt decreased release from the bone marrow. Removal of old red blood cells becomes diminished. Glucocorticoids can cause involution of lymphoid tissue.

GI Tract and Hepatic System: Glucocorticoids increase the secretion of gastric acid, pepsin, and trypsin. They alter the structure of mucin and decrease mucosal cell proliferation. Iron salts and calcium absorption are decreased while fat absorption is increased. Hepatic changes can include increased fat and glycogen deposits within hepatocytes, increased serum levels of alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (GGT). Significant increases can be seen in serum alkaline phosphatase levels. Glucocorticoids can cause minor increases in BSP (bromosulfophthalein) retention time.

Immune System (also see Cells and Hematopoietic System): Glucocorticoids can decrease circulating levels of T-lymphocytes; inhibit lymphokines; inhibit neutrophil, macrophage, and monocyte migration; reduce production of interferon; inhibit phagocytosis and chemotaxis; antigen processing; and diminish intracellular killing. Specific acquired immunity is affected less than nonspecific immune responses. Glucocorticoids can also antagonize the complement cascade and mask the clinical signs of infection. Mast cells are decreased in number and histamine synthesis is suppressed. Many of these effects only occur at high or very high doses and there are species differences in response.