Codeine phosphate may also be known as: codeine phosphate hemihydrate, codeini phosphas; codeini phosphas hemihydricus, or codeinii phosphas; many trade names are available.

Storage/Stability/Compatibility

Codeine phosphate and sulfate tablets should be stored in light-resistant, well-closed containers at room temperature. Codeine phosphate injection should be stored at room temperature (avoid freezing) and protected from light. Do not use the injection if it is discolored or contains a precipitate.

Codeine phosphate injection is reportedly **compatible** with glycopyrrolate or hydroxyzine HCl. It is reportedly **incompatible** with aminophylline, ammonium chloride, amobarbital sodium, chlorothiazide sodium, heparin sodium, methicillin sodium, pentobarbital sodium, phenobarbital sodium, phenytoin sodium, secobarbital sodium, sodium bicarbonate, sodium iodide, and thiopental sodium.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None.

The ARCI (Racing Commissioners International) has designated this drug as a class 1 substance. See the appendix for more information.

HUMAN-LABELED PRODUCTS:

There are many products available containing codeine. The following is a partial listing:

Codeine Phosphate Solution: 15 mg/5 mL in 500 mL & UD 5 mL; Codeine Phosphate (Roxane); (Rx, C-II)

Codeine Sulfate Tablets: 15 mg, 30 mg & 60 mg; generic; (Rx, C-II)

Codeine Phosphate Parenteral Injection: 15 mg/mL & 30 mg/mL in 2 mL *Carpuject* syringe; generic; (Rx, C-II)

Codeine Phosphate Antitussives with expectorants: 10 mg codeine phosphate and 200 mg guaifenesin; 10 mg codeine phosphate and 100 mg guaifenesin; Many different trade names available; (C-V; C-III; certain states may restrict at a higher level; OTC or Rx)

Codeine Phosphate 7.5 mg (#1), 15 mg (#2), 30 mg (#3), 60 mg (#4) with Acetaminophen 300 mg tablets; *Tylenol® with Codeine #'s 1, 2, 3, 4* (McNeil); generic; (Rx, C-III) **WARNING:** Do not use in cats.

Codeine Phosphate 15 mg (#2), 30 mg (#3), 60 mg (#4) with Aspirin 320 mg tablets; *Empirin® with Codeine #'s 2, 3, 4* (Glaxo Wellcome); generic; (Rx, C-III)

Note: Codeine-only products are Class-II controlled substances. Combination products with aspirin or acetaminophen are Class-III. Codeine containing cough syrups are either Class-V or Class-III, depending on the state.

COLCHICINE

(***kol*-chi-seen**)

ANTIINFLAMMATORY

Prescriber Highlights

- **Unique antiinflammatory occasionally used in dogs for hepatic cirrhosis/fibrosis; relatively experimental**
- **Contraindications: Serious renal, GI, or cardiac dysfunction**
- **Caution: Geriatric or debilitated patients**
- **Teratogenic, reduces spermatogenesis**
- **Most likely adverse effects are GI distress (may be an early sign of toxicity), but several serious effects are possible including bone marrow suppression**

Uses/Indications

In veterinary medicine, colchicine has been proposed as a treatment in small animals for amyloidosis. For colchicine to be effective, however, it must be given early in the course of the disease and it will be ineffective once renal failure has occurred. At the time of writing, no conclusive evidence exists for its efficacy for this indication in dogs.

Colchicine has also been proposed for treating chronic hepatic fibrosis presumably by decreasing the formation and increasing the breakdown of collagen.

Pharmacology/Actions

Colchicine inhibits cell division during metaphase by interfering with sol-gel formation and the mitotic spindle. The mechanism for its antifibrotic activity is believed secondary to collagenases activity stimulation.

Colchicine apparently blocks the synthesis and secretion of serum amyloid A (SAA; an acute-phase reactant protein) by hepatocytes thereby preventing the formation of amyloid-enhancing factor and preventing amyloid disposition.

Colchicine is best known in human medicine for its antigout activity. The mechanism for this effect is not fully understood, but it probably is related to the drug's ability to reduce the inflammatory response to the disposition of monosodium urate crystals.

Pharmacokinetics

No information was located specifically for domestic animals; the following information is human/lab animal data unless otherwise noted. After oral administration, colchicine is absorbed from the GI tract. Some of the absorbed drug is metabolized in the liver (first-pass effect). These metabolites and unchanged drug are re-secreted into the GI tract via biliary secretions where it is reabsorbed. This "recycling" phenomena may explain the intestinal manifestations noted with colchicine toxicity. Colchicine is distributed into several tissues, but is concentrated in leukocytes. Plasma half-life is about 20 minutes, but leukocyte half-life is approximately 60 hours. Colchicine is deacetylated in the liver and metabolized in other tissues. While most of a dose (as colchicine and metabolites) is excreted in the feces, some is excreted in the urine. More may be excreted in the urine in patients with hepatic disease. Patients with severe renal disease may have prolonged half-lives.

Contraindications/Precautions/Warnings

Colchicine is contraindicated in patients with serious renal, GI, or cardiac dysfunction and should be used with caution in patients in

early stages of these disorders. It should also be used with caution in geriatric or debilitated patients.

Colchicine use in veterinary medicine is somewhat controversial as safety and efficacy have not been well documented.

Adverse Effects

There has been very little experience with colchicine in domestic animals. There are reports that colchicine can cause nausea, vomiting, and diarrhea in dogs, but these are thought to occur infrequently at doses used. Neutropenia is a rare adverse effect.

In humans, GI effects have been noted (abdominal pain, anorexia, vomiting, diarrhea) and can be an early indication of toxicity; it is recommended to discontinue therapy (in humans) should these occur. Prolonged administration has caused bone marrow depression. Severe local irritation has been noted if extravasation occurs after intravenous administration; thrombophlebitis has also been reported.

Reproductive/Nursing Safety

Because colchicine has been demonstrated to be teratogenic in laboratory animals (mice and hamsters) it should be used during pregnancy only when its potential benefits outweigh its risks. Colchicine may decrease spermatogenesis. In humans, the FDA categorizes this drug as category ***C*** (ORAL) 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 humans, the FDA categorizes this drug as category ***D*** (PARENTERAL) for use during pregnancy (*There is evidence of human fetal risk, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.*)

It is unknown if colchicine enters maternal milk; use cautiously in nursing mothers.

Overdosage/Acute Toxicity

Colchicine can be a very toxic drug after relatively small overdoses. Deaths in humans have been reported with a single oral ingestion of as little as 7 mg, but 65 mg is considered the lethal dose in an adult human. GI manifestations are usually the presenting signs seen. These can range from anorexia and vomiting to bloody diarrhea or paralytic ileus. Renal failure, hepatotoxicity, pancytopenia, paralysis, shock, and vascular collapse may also occur.

There is no specific antidote to colchicine. Gut removal techniques should be employed when applicable. Because of the extensive GI "recycling" of the drug, repeated doses of activated charcoal and a saline cathartic may reduce systemic absorption. Other treatment is symptomatic and supportive. Dialysis (peritoneal) may be of benefit.

Drug Interactions

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

- **BONE MARROW DEPRESSANT MEDICATIONS** (*e.g.,* **antineoplastics, immunosuppressants, chloramphenicol, amphotericin B**): May cause additive myelosuppression when used with colchicine

Laboratory Considerations

- Colchicine may cause false-positive results when testing for **erythrocytes or hemoglobin in urine**.
- Colchicine may interfere with **17-hydroxycorticosteroid** determinations in urine if using the Reddy, Jenkins, and Thorn procedure.
- Colchicine may cause increased serum values of **alkaline phosphatase**.

Doses

Colchicine may have some efficacy in the treatment of amyloidosis, but veterinary dosages are apparently unavailable at this time.

- **DOGS:**

For the adjunctive treatment of hepatic cirrhosis/fibrosis:

a) 0.03 mg/kg PO once daily (Leveille-Webster and Center 1995); (Twedt 1999); (Richter 2002); (Willard 2006b)

b) 0.025–0.03 mg/kg PO once daily (probenecid-free drug). Not recommended for initial use with azathioprine, chlorambucil or methotrexate due to similar side effects (GI toxicity, bone marrow suppression). Used in many dogs and fewer cats without problems. (Center 2002), (Center 2006a)

For amyloidosis:

a) For periodic fever syndrome in Shar Pei dogs: 0.03 mg/kg PO once daily. (Scherk and Center 2005)

b) To reduce the frequency and severity of fever and prevent the development of amyloidosis in dogs with Shar Pei Fever: 0.025–0.03 mg/kg PO q24h; no evidence supports use of colchicine once amyloidosis has resulted in renal failure (Vaden 2006a)

Monitoring

- Efficacy
- Adverse effects (see above)
- CBC

Client Information

- Clients should be informed of the "investigational" nature of colchicine use in dogs and should be informed of the potential adverse effects that may be seen
- Report changes in appetite or other GI effects immediately to veterinarian
- Keep well out of reach of children or pets
- Pregnant women should avoid exposure to the drug or urine of animals being treated

Chemistry/Synonyms

An antigout drug possessing many other pharmacologic effects, colchicine occurs as a pale yellow, amorphous powder or scales. It is soluble in water and freely soluble in alcohol.

Colchicine may also be known as: colchicinum, *Artrex®*, *Colchily®*, *Colchicquim®*, *Colchis®*, *Colcine®*, *Colgout®*, *Goutichine®*, *Goutnil®*, *Reugot®*, *Ticolcin®*, or *Tolchicine®*.

Storage/Stability

Colchicine tablets should be stored in tight, light resistant containers. The injection should be diluted only in 0.9% sodium chloride for injection or sterile water for injection. Do not use D_5W or bacteriostatic sodium chloride for injection as precipitation may occur. Do not use solutions that have become turbid.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

The ARCI (Racing Commissioners International) has designated this drug as a class 4 substance. See the appendix for more information.

HUMAN-LABELED PRODUCTS:

Colchicine Tablets: 0.6 mg (1/100 gr); generic; (Rx);

Colchicine Injection: 0.5 mg/mL in 2 mL vials; Colchicine (Bedford); (Rx)

A combination oral product (tablets) containing colchicine 0.5 mg and probenecid 500 mg is also available (not likely to be useful in veterinary patients)

Co-Trimoxazole; Co-trimazine — See Sulfa/Trimethoprim

CORTICOTROPIN (ACTH)

(kor-ti-koe-***troe***-pin) Acthar®

HORMONAL DIAGNOSTIC AGENT

Prescriber Highlights

- Stimulates cortisol release; used primarily to test for hyper- or hypoadrenocorticism (ACTH-stimulation test)
- Adverse Effects: Unlikely unless using chronically
- Do not administer gel form IV
- Issues include availability & expense

Uses/Indications

Availability of corticotropin in FDA-approved products is an issue as no commercially products were commercially available for veterinary use at the time writing and either cosyntropin (see monograph) or compounded ACTH products are required.

In veterinary medicine, an ACTH product (*Adrenomone*®—Summit Hill) was approved for use in dogs, cats, and beef or dairy cattle for stimulation of the adrenal cortex when there is a deficiency of ACTH and as a therapeutic agent in primary bovine ketosis, but apparently is no longer commercially available. In practice, ACTH tends to be used most often in the diagnosis of hyper- or hypoadrenocorticism (ACTH-stimulation test) and to monitor the response to mitotane therapy in Cushing's syndrome.

One reference (Behrend 2003a) recommends using the ACTH stimulation test if the dog has non-adrenal illness, received any form of exogenous glucocorticoids (including topicals), or received phenobarbital. If the dog has no known non-adrenal illness and moderate to severe clinical signs of hyperadrenocorticism, use the low-dose dexamethasone suppression test. If using the ACTH-stim test, the author states that cosyntropin is the agent of choice (see that monograph).

ACTH has been used for several purposes in human medicine for its corticosteroid stimulating properties, but as it must be injected, it is not commonly employed in veterinary patients.

Pharmacology/Actions

ACTH stimulates the adrenal cortex (principally the zona fasciculata) to stimulate the production and release of glucocorticoids (primarily cortisol in mammals and corticosterone in birds). ACTH release is controlled by corticotropin-releasing factor (CRF) activated in the central nervous system and via a negative feedback pathway, whereby either endogenous or exogenous glucocorticoids suppresses ACTH release.

Pharmacokinetics

Because it is rapidly degraded by proteolytic enzymes in the gut, ACTH cannot be administered PO. It is not effective if administered topically to the skin or eye.

After IM injection in humans, repository corticotropin injection is absorbed over 8–16 hours. The elimination half-life of circulating ACTH is about 15 minutes but because of the slow absorption after IM injection of the gel, effects may persist up to 24 hours.

Contraindications/Precautions/Warnings

When used for diagnostic purposes, it is unlikely that increases in serum cortisol levels induced by ACTH will have significant deleterious effects on conditions where increased cortisol levels are contraindicated (*e.g.*, systemic fungal infections, osteoporosis, peptic ulcer disease, etc.). ACTH gel should not be used in patients hypersensitive to porcine proteins.

Adverse Effects

Prolonged use may result in fluid and electrolyte disturbances and other adverse effects; if using on a chronic basis, refer to the human literature for an extensive listing of potential adverse reactions. The veterinary manufacturer suggests giving potassium supplementation with chronic therapy.

Do not administer the repository form (gel) IV.

Reproductive/Nursing Safety

ACTH should only be used during pregnancy when the potential benefits outweigh the risks. It may be embryocidal. Neonates born from mothers receiving ACTH should be observed for signs of adrenocortical insufficiency. In humans, the FDA categorizes this drug 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.*)

Overdosage/Acute Toxicity

When used for diagnostic purposes, acute inadvertent overdoses are unlikely to cause any significant adverse effects. Monitor as required and treat symptomatically if necessary.

Drug Interactions

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

- **ANTICHOLINESTERASES** (*e.g.*, **pyridostigmine**): ACTH may antagonize effects in patients with myasthenia gravis
- **DIURETICS:** ACTH may increase electrolyte loss

Laboratory Considerations

- Patients should not receive **hydrocortisone** or **cortisone** on test day
- ACTH may decrease **^{131}I uptake** by the thyroid gland
- ACTH may suppress **skin test reactions**
- ACTH may interfere with **urinary estrogen** determinations
- Obtain specific information from the laboratory on sample handling and laboratory normals for cortisol when doing ACTH stimulation tests

Doses

Note: When using compounded ACTH products, it is recommended to get several post-ACTH samples, at a minimum one and two hours following injection. (Behrend 2005)

- **DOGS:**

  ACTH Stimulation Test:

  a) Draw baseline blood sample for cortisol determination and administer 2.2 Units/kg of ACTH gel IM. Draw sample 120 minutes after injection. (Feldman and Peterson 1984), (Kemppainen and Zerbe 1989b)