SILDENAFIL CITRATE

(sil-***den***-ah-fil) Viagra®, Revatio®

VASODILATOR; PHOSPHODIESTERASE TYPE 5 INHIBITOR

Prescriber Highlights

- Used in veterinary medicine for treating pulmonary hypertension
- Contraindicated if patients receiving organic nitrates
- Adverse effects not well-known; inguinal flushing, possible GI effects reported
- Treatment may be very expensive

Uses/Indications

Sildenafil may be of benefit in the adjunctive treatment of pulmonary hypertension in small animals.

In humans, sildenafil is indicated for erectile dysfunction or pulmonary hypertension.

Pharmacology/Actions

Sildenafil inhibits cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type-5 (PDE5) found in the smooth muscle of the pulmonary vasculature, corpus cavernosum and elsewhere, where PDE5 is responsible for degradation of cGMP. Sildenafil increases cGMP thereby resulting in nitric oxide mediated vasodilatation within pulmonary vascular smooth muscle cells.

Pharmacokinetics

The pharmacokinetics of sildenafil has been reported in dogs (Walker, Ackland et al. 1999). Oral bioavailability is approximately 50% (higher than humans); volume of distribution is about 5.2 L/kg (versus 1.2 L/kg in humans); elimination half-life approximately 6 hours (significant interpatient variability; average human half life is about 4 hours).

Contraindications/Precautions/Warnings

Sildenafil should not be used concurrently with nitrates (see drug interactions) or in patients documented hypersensitive to it.

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD).

Use with extreme caution in patients with resting hypotension, fluid depletion, severe left ventricular outflow obstruction, or autonomic dysfunction.

Adverse Effects

Because of limited use in dogs, the adverse effect profile is not fully known. Cutaneous flushing of the inguinal region has been reported and GI effects are possible. In humans, headache, visual disturbances, dyspepsia, nasal congestion, myalgia, priapism, dizziness, and back pain have been reported.

Reproductive/Nursing Safety

No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in pregnant rats or rabbits, dosed at 200 mg/kg/day during organogenesis. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day. 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.*)

It is not known if sildenafil or its metabolites are excreted in milk.

Overdosage/Acute Toxicity

Little information is available. An adult women ingested 2000 mg and survived but developed tachycardia, nonspecific ST-T changes on ECG, headache, dizziness, and flushing.

It is expected that overdoses in animals would mirror the drugs adverse effect profile; treat supportively.

Drug Interactions

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

- **ALPHA-ADRENERGIC BLOCKERS** (*e.g.,* **phentolamine, phenothiazines, phenoxybenzamine**): May increase hypotensive effects
- **AMLODIPINE:** Potential to increase hypotensive effects
- **ANTIHYPERTENSIVE, HYPOTENSIVE DRUGS:** Potentially could increase hypotensive effects
- **AZOLE ANTIFUNGALS** (**ketoconazole, itraconazole**): May reduce sildenafil metabolism and increase AUC
- **CIMETIDINE:** May reduce sildenafil metabolism and increase AUC
- **ERYTHROMYCIN, CLARITHROMYCIN:** May reduce sildenafil metabolism and increase AUC
- **HEPARIN:** May increase bleeding risks
- **NITRATES** (*e.g.,* **NTG, Isosorbide**): Significant potentiation of vasodilatory effects; life-threatening hypotension possible
- **NITROPRUSSIDE SODIUM:** Significant potentiation of vasodilatory effects; life-threatening hypotension possible
- **PHENOBARBITAL:** May decrease sildenafil concentrations
- **RIFAMPIN:** May decrease sildenafil concentrations

Laboratory Considerations

None were noted.

Doses

- **DOGS/CATS:**

  Dogs: From a retrospective study: median dose was 1.9 mg/kg (range from 0.5–2.7 mg/kg) q8–24h. Dogs may have been also treated with oxygen, ACE inhibitors, furosemide, amlodipine, diltiazem, theophylline, phenobarbital and/or antibiotics. (Bach, Rozanski et al. 2006)

  For pulmonary hypertension documented by Doppler, chronic pulmonary disease, right-sided heart failure (HW disease; congenital): 0.5–1 mg/kg PO two times daily (higher dose of 2–3 mg/kg three times a day may be tolerated and needed) (Tilley 2007)

Monitoring

- Clinical efficacy (improved syncope, cough, respiratory effort)
- Pulmonary artery pressure, systemic blood pressure

Client Information

- Brief clients on the experimental nature of using this medication in small animals and the costs of therapy

Chemistry/Synonyms

Sildenafil citrate occurs as a white to off-white crystalline powder with a solubility of 3.5 mg/mL in water and a molecular weight of 666.7.

Sildenafil may also be known as UK 92480, UK 92480-10, *Aphrodil*®, *Revatio*®, or *Viagra*®.

Storage/Stability
Sildenafil tablets should be stored at room temperature (25°C; 77°F); excursions permitted to 15–30°C (59–86°F).

Dosage Forms/Regulatory Status
VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Sildenafil Citrate Tablets: 20 mg (of sildenafil); *Revatio*® (Pfizer); (Rx)

Sildenafil Citrate Tablets: 25 mg, 50 mg & 100 mg (of sildenafil); *Viagra*® (Pfizer); (Rx)

SILYMARIN
MILK THISTLE

(sill-e-***mar***-in) Marin®

NUTRACEUTICAL HEPATO-PROTECTANT

Prescriber Highlights

- Nutraceutical that may be useful for treatment of chronic & acute liver disease, cirrhosis; as a hepato-protective agent when hepatotoxins (*e.g.*, *Aminita phalloide*) ingested
- Appears well-tolerated; potentially could cause GI effects
- Do not confuse Milk Thistle with Blessed Thistle
- Potential drug interactions

Uses/Indications
While controlled studies demonstrating efficacy and a standardized form and concentration of silymarin are lacking, it is being used to treat a variety of liver diseases in humans and domestic companion animals (birds, dogs, cats, horses, rabbits). It is mostly of interest in treating chronic and acute liver disease, cirrhosis, and as a hepato-protective agent when hepatotoxic agents are ingested (*e.g.*, *Aminita phalloide*; "Death Cap Mushrooms").

Pharmacology/Actions
Silymarin has a variety of pharmacologic actions that may contribute to its apparent effects in treating liver disease. It inhibits lipid peroxidase and beta-glucoronidase and acts as an anti-oxidant and free radical scavenger. Silymarin also inhibits the cytotoxic, inflammatory, and apoptotic effects of tumor necrosis factor (TFN). It apparently can alter outer hepatocyte cell membranes that can prevent toxin penetration. Silymarin is thought to reduce hepatic collagen formation and increase hepatic glutathione content.

Pharmacokinetics
In humans, silymarin has an oral bioavailability of less than 50% and peak levels occur 2–4 hours post-dose. When silibinin (silybin, sylibin) is complexed with phosphatidylcholine, oral absorption can be increased. The drug undergoes extensive enterohepatic circulation and has significantly higher concentrations in liver cells and bile than in plasma. Elimination half-life in humans averages 6 hours. The majority of the drug is eliminated unchanged in the feces, but 20–40% is converted into glucuronide and sulfate conjugates which are eliminated in the feces; only about 8% is excreted in the urine.

Contraindications/Precautions/Warnings
There are no reported absolute contraindications to silymarin in animals. Extracts from the plant parts of Milk Thistle (not the seeds which are used to make the extract silymarin), may possess estrogen-like activity and should not be used in patients where exogenous estrogens would be contraindicated.

Adverse Effects
Silymarin is apparently well tolerated when administered orally. In humans, GI disturbances have been reported on occasion (nausea to diarrhea). Patients who have allergies to other members of the Asteraceae/Compositae plant family (includes ragweed, marigolds, daisies, etc.) may exhibit allergic reactions to Milk Thistle derivatives. Do not confuse Milk Thistle with Blessed Thistle.

Reproductive/Nursing Safety
Data on the safety of silymarin use during pregnancy or nursing is not available; its potential benefit must be weighed against the uncertainty of its safety.

Overdosage/Acute Toxicity
Overdoses are unlikely to cause significant morbidity. Gastrointestinal effects may be seen and treated in a supportive manner.

Drug Interactions
While no specific drug interactions have been reported, silymarin may inhibit cytochrome P450 isoenzyme 2C9 (CYP2C9). Drugs with narrow therapeutic indexes that are metabolized by this isoenzyme should be used with caution when using silymarin. Drugs that could be affected include: **warfarin, amitriptyline, verapamil,** etc.

Silymarin also may inhibit CYP3A4, but thus far this interaction does not appear to be clinically significant. Silymarin may increase the clearance of drugs that undergo hepatic glucuronidation (not cats), including: **acetaminophen, diazepam, morphine, and lamotrigine.** Clinical significance has not been determined for this interaction and the usefulness of silymarin for treating acetaminophen toxicity has not been determined.

Laboratory Considerations
No interactions with laboratory tests are reported.

Doses
- **DOGS & CATS:**
  a) Therapeutic dosage is unknown, but suggested doses range from 50–250 mg/day (Twedt 2004)
  b) For adjunctive therapy for chronic liver disease: 20–50 mg/kg per day (extrapolated from human, monkey, rodent and dog research) (Center 2002)
  c) For chronic liver disease and ameliorating the effects of anticonvulsants: Dosages vary from 50–200 mg given every 12–24 hours (Tams 2001)
  d) For hepatotoxicity, hepatic recovery/regeneration, hepatic fibrosis: 20–50 mg/kg/day. (Webb 2007b)
  e) Cats: 4–8 mg/kg/day (Zoran 2006b)

Monitoring
- Clinical efficacy

Client Information
- Because silymarin experience in animals is limited, clients should understand the "investigational nature" of its use

Chemistry/Synonyms
Milk Thistle, the common name for *Silybum marianum*, has been used as a medicinal agent for at least two thousand years. The me-