Reproductive/Nursing Safety

There is little information on the reproductive safety of calcitonin; however, it does not cross the placenta. Very high doses have decreased birth weights in laboratory animals, presumably due to the metabolic effects of the drug. 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.*)

Calcitonin has been shown to inhibit lactation. Safe use during nursing has not been established.

Overdosage/Acute Toxicity

Very limited data is available. Nausea and vomiting have been reported after accidental overdose injections. Chronic overdosing can lead to hypocalcemia.

Drug Interactions

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

- **VITAMIN D ANALOGS** or **CALCIUM** products: May interfere with the efficacy of calcitonin

Doses

- **DOGS:**

For hypervitaminosis D (toxicity)/hypercalcemia:

a) 4–6 IU/kg SC q12h to q8h (Carothers, Chew et al. 1994)

b) In animals with severe hypercalcemia (>16 mg/dL) calcitonin may be beneficial when used in combination with furosemide, IV fluids, and prednisone. Initially, give 4 U/kg IV, followed by 4–8 mg/kg SC once or twice daily (dose extrapolated from human information) (Carothers, Chew et al. 1994)

c) 4–6 IU/kg SC q2–3 hours until serum calcium levels are normalized (Firth 2000)

d) For adjunctive therapy if fluid deficit replacement, saline diuresis, furosemide and prednisone have failed to control calcium: 4 Units/kg IV, then 4–8 U/kg SC q12–24h (Nelson and Elliott 2003b)

e) 4–6 Units/kg SC q8–12h (Davies 2005)

- **REPTILES:**

For hypercalcemia:

a) Green iguanas in combination with fluid therapy: 1.5 IU/kg SC q8h for several weeks if necessary (Gauvin 1993)

For secondary nutritional hyperparathyroidism or nutritional secondary hyperparathyroidism (NSHP):

a) If reptile is not hypocalcemic: 50 Units/kg IM once weekly for 2–3 doses. (Hernandez-Divers 2005)

b) Correct husbandry problems and correct hypocalcemia with calcium and vitamin D. Once calcium level is normal and patient is on oral calcium supplementation (usually about 7 days after starting therapy) give calcitonin at 50 Units/kg IM weekly for 2–3 doses. Supportive care can be tapered off once patient becomes stable. (Johnson 2004a)

Monitoring

- Serum Calcium

Chemistry/Synonyms

A polypeptide hormone, calcitonin is a 32-amino acid polypeptide having a molecular weight of about 3600. Calcitonin is available commercially as either calcitonin human or calcitonin salmon, both of which are synthetically prepared. Potency of calcitonin salmon is expressed in international units (IU). Calcitonin salmon is approximately 50X more potent than calcitonin human on a per weight basis.

Calcitonin salmon may also be known as calcitonin-salmon, calcitoninum salmonis, salmon calcitonin, SCT-1, or *Calcimar®*; many other trade names are available internationally.

Storage/Stability

Calcitonin salmon for injection should be stored in the refrigerator (2–8°C). The nasal solution should be stored in the refrigerator but protected from freezing. Once in use it should be stored at room temperature in an upright position; use within 35 days.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Calcitonin Salmon for Injection: 200 IU/mL in 2 mL vials; *Miacalcin®* (Novartis); (Rx)

Calcitonin Salmon Intranasal Spray: 200 Units/activation (0.09 mL/dose) in 2 mL (*Miacalcin®*) and 3.7 mL (*Fortical®*) glass bottles with pump; *Miacalcin®* (Novartis); *Fortical®* (Upsher-Smith); (Rx)

CALCITRIOL

(kal-si-*trye*-ole) Rocaltrol®, Calcijex®

VITAMIN D ANALOG

Prescriber Highlights

- **Vitamin D analog may be useful in dogs (& possibly cats) for treatment of hypocalcemia, chronic renal disease or idiopathic seborrhea.**
- **Contraindications: Hypercalcemia, hyperphosphatemia, malabsorption syndromes**
- **Adverse Effects: Hypercalcemia, hypercalcuria or hyperphosphatemia greatest concerns**
- **May need to have oral dosage forms compounded**
- **Do not confuse with calcitonin**

Uses/Indications

Calcitriol may be potentially beneficial in the adjunctive treatment of chronic renal disease in dogs and cats but its use is somewhat controversial, particularly the decision on how soon in the course of chronic renal insufficiency it should employed. It may also be of benefit in treating some types of dermatopathies (primary idiopathic seborrhea).

Pharmacology/Actions

Calcitriol is a vitamin D analog. Vitamin D is considered a hormone and, in conjunction with parathormone (PTH) and calcitonin, regulates calcium homeostasis in the body. Active analogues (or metabolites) of vitamin D enhance calcium absorption from the GI tract, promote reabsorption of calcium by the renal tubules, and increase the rate of accretion and resorption of minerals in bone. Calcitriol has a rapid onset of action (approximately 1 day) and a short dura-

tion of action. Unlike other forms of vitamin D, calcitriol does not require renal activation for it to be effective.

Pharmacokinetics

If fat absorption is normal, vitamin D analogs are readily absorbed from the GI tract (small intestine). Bile is required for adequate absorption and patients with steatorrhea, liver or biliary disease will have diminished absorption. Calcitriol has a rapid onset of biologic action and has a short duration of action (<1 day to 2–3 days). Dogs and cats appear to require much smaller doses of calcitriol than do humans.

Contraindications/Precautions/Warnings

Calcitriol is contraindicated in patients with hypercalcemia, vitamin D toxicity, malabsorption syndrome, or abnormal sensitivity to the effects of vitamin D. It should be used with extreme caution in patients with hyperphosphatemia (many clinicians believe hyperphosphatemia or a combined calcium/phosphorous product of >70 is a contraindication to the use of vitamin D analogs).

Adverse Effects

While hypercalcemia is a definite concern, calcitriol administered in low dosages to dogs with chronic renal disease infrequently causes hypercalcemia, unless it is used with a calcium-containing phosphorus binder, particularly calcium carbonate. Signs of hypercalcemia include polydipsia, polyuria and anorexia. Hyperphosphatemia may also occur and patients' serum phosphate levels should be normalized before therapy is begun. Monitoring of serum calcium levels is mandatory while using this drug.

Reproductive/Nursing Safety

Calcitriol has proven to be teratogenic in laboratory animal when given at doses several times higher than those used therapeutically. 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.*)

Safe use during lactation has not been established.

Overdosage/Acute Toxicity

Overdosage can cause hypercalcemia, hypercalciuria, and hyperphosphatemia. Intake of excessive calcium and phosphate may also cause the same effect. Acute ingestions should be managed using established protocols for removal or prevention of the drug being absorbed from the GI. Orally administered mineral oil may reduce absorption and enhance fecal elimination.

Hypercalcemia secondary to chronic dosing of the drug should be treated by first temporarily discontinuing (not dose reduction) calcitriol and exogenous calcium therapy. If the hypercalcemia is severe, furosemide, calcium-free IV fluids (*e.g.*, normal saline), urine acidification, and corticosteroids may be employed.

Drug Interactions

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

- **CALCIUM-CONTAINING PHOSPHORUS BINDING AGENTS** (*e.g.,* **calcium carbonate**): Use with calcitriol may induce hypercalcemia
- **CORTICOSTEROIDS:** Can nullify the effects of vitamin D analogs
- **DIGOXIN or VERAPAMIL:** Patients on verapamil or digoxin are sensitive to the effects of hypercalcemia; intensified monitoring is required
- **PHENYTOIN, BARBITURATES or PRIMIDONE:** May induce hepatic enzyme systems and increase the metabolism of Vitamin D analogs thus decreasing their activity
- **THIAZIDE DIURETICS:** May cause hypercalcemia when given in conjunction with Vitamin D analogs

Laboratory Considerations

- **SERUM CHOLESTEROL** levels may be falsely elevated by vitamin D analogs when using the Zlatkis-Zak reaction for determination

Doses

- **DOGS:**

  To suppress secondary hyperparathyroidism in CRF:

  a) Decision to use calcitriol must be made with caution because hypercalcemia is potentially a serious complication that if prolonged can result in a reduction (reversible or irreversible) of GFR. Hypercalcemia is an uncommon side effect (unless used with a calcium-containing phosphorus binding agent) if calcitriol is dosed at 2.5–3.5 ng/kg/day PO. (Polzin, Osborne et al. 2005)

  b) 2.5–3.5 ng/kg PO once daily. Dogs with refractory hyperparathyroidism may require up to 6 ng/kg/day. (Chew 2003)

  c) **1)** Confirm the diagnosis of chronic renal failure (serum creatinine >2 mg/dl); **2)** Reduce hyperphosphatemia to <6 mg/dl; 3) If serum creatinine between 2–3 mg/dl and serum phosphorus <6 mg/dl, start calcitriol at 2.5–3.5 ng/kg/day PO (so-called "preventative" dose); if serum creatinine >3 mg/dl and serum phosphorus <6 mg/dl, obtain a baseline PTH level and start calcitriol at 3.5 ng/kg/day.

  Monitoring of preventative dose: assess serum calcium on days 7 and 14 after starting calcitriol and then every 6 months. Serum creatinine should be measured every 1–3 months. If hypercalcemia occurs, stop calcitriol for one week to determine if the drug is causing the hypercalcemia or if it's due to another cause (*e.g.,* too little calcitriol).

  Monitoring patients with elevated PTH: monitor as above, but also determine PTH levels at 4–6 weeks after starting calcitriol. If still elevated increase dose by 1–2 ng/kg/day, but do not exceed 6.6 ng/kg/day unless monitoring ionized calcium. If higher daily doses are required (5–7 ng/kg/day), a pulsed-dosing strategy may be considered. This is usually about 20 ng/kg given twice weekly PO at bedtime on an empty stomach. (Nagode 2005)

  For subacute and chronic maintenance treatment of hypocalcemia:

  a) Initially, 20–30 ng/kg/day PO divided twice a day for 3–4 days, then 5–15 ng/kg/day divided twice a day (Chew and Nagode 2000)

  For primary idiopathic seborrhea (especially in spaniel breeds):

  a) 10 ng/kg PO once daily. Give as far away from the main meal as possible. (Kwochka 1999)

- **CATS:**

  To suppress secondary hyperparathyroidism in CRF:

  a) 1.65–3.63 ng/kg PO daily (Polzin, Osborne et al. 2000)

  b) 2.5–3.5 ng/kg PO once daily (Chew 2003)

  c) See the dog dose in "c" above (Nagode 2005)

Monitoring

- Serum calcium, phosphate, creatinine. Baseline and at one week and 1 month after starting treatment; then monthly thereafter
- Urine calcium baseline and as needed
- Serum PTH levels
- Clinical efficacy (*e.g.*, improved appetite, activity level, slowed progression of disease)

Client Information
- Clients should be briefed on the signs of hypercalcemia (polydipsia, polyuria, anorexia) and hypocalcemia (muscle tremors, twitching, tetany, weakness, stiff gait, ataxia, behavioral changes, and seizures) and instructed to report these signs to the veterinarian
- If using lower doses (<3.5 ng/kg/day) give with the morning meal; if using doses of >5 ng/kg/day; administer at bedtime on an empty stomach to reduce chance for hypercalcemia

Chemistry/Synonyms
Calcitriol, a vitamin D analog is synthesized for pharmaceutical use. It is a white crystalline compound and is insoluble in water.

Calcitriol may also be known as: calcitrolo, calcitriolum, 1,25-dihydroxycholecalciferol, 1-alpha,25 dihydrocholecalciferol, 1alpha, 25-Dihydroxyvitamin D_3 or 1,25-DHCC, 1,25-dihidroxyvitamin D_3, Ro 21-5535, U 49562, *Acuode®, Alpha D_3®, Bocatriol®, Calcijex®, Calcitriol KyraMed®, Calcitriol Purissimus®, Calcitriol-Nefro®, Calcitriolo®, Decostriol®, Dexiven®, Difix®, Hitrol®, Kalcytriol®, Kolkatriol®, Lotravel®, Osteotriol®, Renatriol®, Rexamat®, Rocaltrol®, Roical®, Rolsical®, Silkis®, Sitriol®,* or *Tirocal®*.

Storage/Stability
Protect from light. Store in tight, light resistant containers at room temperature. The injection does not contain preservatives and remaining drug should be discarded after opening ampule.

Dosage Forms/Regulatory Status
VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Note: Most doses are expressed in nanograms/kg (ng/kg); to convert mcg to ng: 1 mcg = 1000 ng, 0.25 mcg = 250 ng, etc. Reformulation by a compounding pharmacy is usually required to assure accurate dosing.

Calcitriol Capsules: 0.25 mcg, 0.5 mcg; *Rocaltrol®* (Roche); Calcitriol (Teva); (Rx)

Calcitriol Oral Solution: 1 mcg/mL in 15 mL btls; *Rocaltrol®* (Roche); Calcitriol (Teva); (Rx)

Calcitriol Injection: 1 mcg/mL & 2 mcg/mL in 1 mL amps & vials; *Calcijex®* (Abbott); Calcitriol Injection (aaiPharma); (Rx)

CALCIUM ACETATE

(***kal***-see-um ass-a-***tate***) PhosLo®

ORAL PHOSPHATE BINDER

Prescriber Highlights
- Oral phosphorus binding agent for use in treating hyperphosphatemia associated with chronic renal failure
- Must monitor serum phosphorus & calcium

Uses/Indications
Calcium acetate can be used for oral administration to treat hyperphosphatemia in patients with chronic renal failure. Secondary to its phosphorus binding efficiency and lower concentration of elemental calcium, calcium acetate is considered the most effective and having the lowest potential for causing hypercalcemia of the calcium-based phosphorus-binding agents. When compared to calcium carbonate, calcium acetate binds approximately twice as much phosphorus per gram of elemental calcium administered. Unlike calcium citrate, calcium acetate does not promote aluminum absorption.

Pharmacology/Actions
When calcium acetate is given with meals it binds to dietary phosphorus and forms calcium phosphate, an insoluble compound that is eliminated in the feces. Calcium acetate is soluble over a range of pH and, therefore, available for binding phosphorus in the stomach and proximal small intestine.

Pharmacokinetics
No information was located on the pharmacokinetics of calcium acetate in dogs and cats. In humans, approximately 30% is absorbed when given with food.

Contraindications/Precautions/Warnings
This agent should not be used when hypercalcemia is present. Because hypercalcemia can result from administering oral calcium products to animals with renal failure, adequate monitoring of serum ionized calcium and phosphorus is required.

Use calcium containing phosphate binders with caution in patients having a serum calcium and phosphorus product greater than 60.

Using calcium-based phosphate binders and calcitriol together is controversial. Some authors state the combination is contraindicated; while others state that intensified monitoring for hypercalcemia is required.

Adverse Effects
Hypercalcemia is the primary concern associated with using high dosages of this agent; adequate monitoring is required.

In humans, GI intolerance (nausea) has been reported.

Reproductive/Nursing Safety
No reproductive safety studies were located and the human label states that it is not known whether the drug can cause fetal harm. However, it would be surprising if calcium acetate caused teratogenic effects. In humans, the FDA categorizes calcium acetate 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.*)

It would be expected that calcium acetate would be safe to administer during lactation.

Overdosage/Acute Toxicity
Potentially, acute overdoses could cause hypercalcemia. Patients should be monitored and treated symptomatically. If dosage was massive and recent, consider using standard protocols to empty the gut.

Drug Interactions
The following drug interactions have either been reported or are theoretical in humans or animals receiving calcium acetate and may be of significance in veterinary patients:
- **CALCITRIOL:** If administered with calcium acetate, may lead to hypercalcemia; if calcitriol is used concomitantly, intensified monitoring for hypercalcemia is mandatory
- **DIGOXIN:** Calcium acetate is not recommended for use in human patients that are on digoxin therapy, as hypercalcemia may cause serious arrhythmias
- **FLUOROQUINOLONES, TETRACYCLINES:** Oral calcium-containing products can reduce absorption of fluoroquinolones; if both calcium acetate and one of these antibiotics are required, separate dosages by at least two hours