LEVOTHYROXINE SODIUM

(lee-voe-thye-***rox***-een) Soloxine®, Synthroid®

THYROID HORMONE

Prescriber Highlights

- Thyroid hormone for hypothyroidism in all species
- Contraindications: Acute myocardial infarction, thyrotoxicosis, or untreated adrenal insufficiency
- Caution: Concurrent hypoadrenocorticism (treated), cardiac disease, diabetes, or elderly patients
- Adverse Effects: Only associated with OD's (tachycardia, polyphagia, PU/PD, excitability, nervousness, & excessive panting); some cats may appear apathetic
- Drug-drug; drug-lab interactions

Uses/Indications

Levothyroxine sodium is indicated for the treatment of hypothyroidism in all species.

Pharmacology/Actions

Thyroid hormones affect the rate of many physiologic processes including: fat, protein, and carbohydrate metabolism, increasing protein synthesis, increasing gluconeogenesis, and promoting mobilization and utilization of glycogen stores. Thyroid hormones also increase oxygen consumption, body temperature, heart rate and cardiac output, blood volume, enzyme system activity, and growth and maturity. Thyroid hormone is particularly important for adequate development of the central nervous system. While the exact mechanisms how thyroid hormones exert their effects are not fully understood, it is known that thyroid hormones (primarily triiodothyronine) act at the cellular level.

In humans, triiodothyronine (T_3) is the primary hormone responsible for activity. Approximately 80% of T_3 found in the peripheral tissues is derived from thyroxine (T_4) which is the principle hormone released by the thyroid.

Pharmacokinetics

In dogs, peak plasma concentrations after oral dosing reportedly occur 4–12 hours after administration and the serum half-life is approximately 12–16 hours. There is wide variability from animal to animal, however.

Contraindications/Precautions/Warnings

Levothyroxine (and other replacement thyroid hormones) are contraindicated in patients with acute myocardial infarction, thyrotoxicosis, or untreated adrenal insufficiency. It should be used with caution, and at a lower initial dosage, in patients with concurrent hypoadrenocorticism (treated), cardiac disease, diabetes, or in those who are aged.

Adverse Effects

When administered at an appropriate dose to patients requiring thyroid hormone replacement, there should not be any adverse effects associated with therapy. For adverse effects associated with overdosage, see below.

Reproductive/Nursing Safety

In humans, the FDA categorizes this drug as category ***A*** for use during pregnancy (*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.*)

Minimal amounts of thyroid hormones are excreted in milk and should not affect nursing offspring.

Overdosage/Acute Toxicity

Chronic overdosage will produce signs of hyperthyroidism, including tachycardia, polyphagia, PU/PD, excitability, nervousness and excessive panting. Dosage should be reduced and/or temporarily withheld until signs subside. Some (10%?) cats may exhibit signs of "apathetic" (listlessness, anorexia, etc.) hyperthyroidism.

A single acute overdose in small animals is less likely to cause severe thyrotoxicosis than with chronic overdosage. Vomiting, diarrhea, hyperactivity to lethargy, hypertension, tachycardia, tachypnea, dyspnea, and abnormal pupillary light reflexes may be noted in dogs and cats. In dogs, clinical signs may appear within 1–9 hours after ingestion. If ingestion occurred within 2 hours, treatment to reduce absorption of drug should be accomplished using standard protocols (emetics, cathartics, charcoal) unless contraindicated by the patient's condition. Treatment is supportive and symptomatic. Oxygen, artificial ventilation, cardiac glycosides, beta-blockers (*e.g.*, propranolol), fluids, dextrose, and antipyretic agents have all been suggested for use if necessary; contact an animal poison control center for further guidance.

Drug Interactions

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

- **AMIODARONE:** May decrease the metabolism of T4 to T3
- **ANTACIDS, ORAL:** May reduce levothyroxine absorption; separate doses by 4 hours
- **ANTIDEPRESSANTS, TRICYCLIC/TETRACYCLIC:** Increased risk for CNS stimulation and cardiac arrhythmias
- **ANTIDIABETIC AGENTS** (**insulin, oral agents**): Levothyroxine may increase requirements for insulin or oral agents
- **CHOLESTYRAMINE:** May reduce levothyroxine absorption; separate doses by 4 hours
- **CORTICOSTEROIDS** (high dose): Decreased conversion of T4 to T3
- **DIGOXIN:** Potential for reduced digoxin levels
- **FERROUS SULFATE:** May reduce levothyroxine absorption; separate doses by 4 hours
- **HIGH FIBER DIET:** May reduce levothyroxine absorption
- **KETAMINE:** May cause tachycardia and hypertension
- **PHENOBARBITAL:** Possible increased metabolism of thyroxine; dosage adjustments may be needed
- **PROPYLTHIOURACIL:** Decreased conversion of T4 to T3
- **RIFAMPIN:** Possible increased metabolism of thyroxine; dosage adjustments may be needed
- **SERTRALINE:** May increase levothyroxine requirements
- **SUCRALFATE:** May reduce levothyroxine absorption; separate doses by 4 hours
- **SYMPATHOMIMETIC AGENTS** (**epinephrine**, **norepinephrine**, etc.): Levothyroxine can potentiate effects
- **WARFARIN:** Thyroid hormones increase the catabolism of vitamin K-dependent clotting factors that may increase the anticoagulation effects in patients on warfarin

Laboratory Considerations

The following drugs may have effects on thyroid function tests; evaluate results accordingly:

- **EFFECTS ON SERUM T_4**: aminoglutethimide↓, anabolic steroids/androgens↓, antithyroid drugs (PTU, methimazole)↓, asparaginase↓, barbiturates↓, corticosteroids↓, danazol↓, diazepam↓, estrogens↑ (**Note:** estrogens may have no effect on canine T_3 or T_4 concentrations), fluorouracil↑, heparin↓, insulin↑, lithium carbonate↓, mitotane (o,p-DDD)↓, nitroprusside↓, phenylbutazone↓, phenytoin↓, propranolol↑, salicylates (large doses)↓, and sulfonylureas↓.
- **EFFECTS ON SERUM T_3**: antithyroid drugs (PTU, methimazole)↓, barbiturates↓, corticosteroids↓, estrogens↑, fluorouracil↑, heparin↓, lithium carbonate↓, phenytoin↓, propranolol↓, salicylates (large doses)↓, and thiazides↑.
- **EFFECTS ON T_3 UPTAKE RESIN:** anabolic steroids/androgens↑, antithyroid drugs (PTU, methimazole)↓, asparaginase↑, corticosteroids↑, danazol↑, estrogens↓, fluorouracil↓, heparin↑, lithium carbonate↓, phenylbutazone↑, and salicylates (large doses)↑.
- **EFFECTS ON SERUM TSH:** aminoglutethimide↑, antithyroid drugs (PTU, methimazole)↑, corticosteroids↓, danazol↓, and lithium carbonate↑.
- **EFFECTS ON FREE THYROXINE INDEX (FTI)**: antithyroid drugs (PTU, methimazole)↓, barbiturates↓, corticosteroids↓, heparin↑, lithium carbonate↓, and phenylbutazone↓.

Doses

- **DOGS:**

  For hypothyroidism:

  a) Use a trade name product. Initially give 20 micrograms/kg (0.02 mg/kg) body weight PO twice daily with a maximum dose of 0.8 mg twice daily. Four to eight weeks later evaluate clinical response and draw a T4 level 4–6 hours post dosing.

  If positive clinical response and **1**) low normal T4: increase dose and recheck in 4 weeks; **2**) high normal to slightly higher than normal T4: no change in dosing and recheck in 6 months; **3**) 40% or more greater than high normal: decrease dose or consider once a day therapy and recheck in 4 weeks (if once a day dosing get a level prior to dosing as well).

  If a negative clinical response and **1**) low normal T4: increase dose and recheck in 8 weeks (may need to: increase dose again; change to 3 times a day dosing or reevaluate diagnosis); **2**) high normal to 40% or more greater than high normal: re-evaluate diagnosis.

  For myxedema coma: 5 mcg/kg IV q12h initially as oral administration may be poorly absorbed (Scott-Moncrieff and Guptill-Yoran 2000)

  b) Initiate treatment at 22 micrograms/kg PO twice daily (0.1 mg/10 lbs body weight twice daily); reevaluate dosage after monitoring clinical response and serum levels after 4–8 weeks. If clinical response is satisfactory and T4 is elevated (≥ 60 nmol/L) may reduce dosage to 22 micrograms/kg once daily. If clinical response is not satisfactory, either reevaluate the need for T4 supplementation or increase the dose. Daily dosage of 20–40 micrograms/day appears to be adequate for most dogs. (Refsal and Nachreiner 1995)

  c) 0.022 mg/kg (22 mcg/kg) PO twice daily or 0.044/kg mg (44 mcg/kg) once daily. Monitor by resolution of clinical signs, pre- and post dosing Total T4 (in the normal range), or by endogenous TSH concentrations that decrease into the normal range. (Greco 1999)

  d) 0.02 mg/kg PO twice daily to start; (0.02–0.04 mg/kg PO once daily or, if necessary divided twice daily to maintain). Alternatively, give 0.5 mg/m2 which may prevent hyperthyroid effects, particularly in large breed dogs. (Ferguson 2002)

- **CATS:**

  For hypothyroidism:

  a) 0.05–0.1 mg per cat PO once daily. Monitoring and dosage adjustments as above for dogs. (Scott-Moncrieff and Guptill-Yoran 2000)

  b) Initially, 0.05–0.1 mg once daily. Wait a minimum of 4–6 weeks to assess cat's clinical response to treatment. Then obtain a serum T_4 level prior to, and 6–8 hours after, dosing. Increase or decrease dose and/or dosing frequency after reviewing these values and clinical response. If levothyroxine is ineffective, may try liothyronine. (Feldman and Nelson 1987d)

- **HORSES:**

  For hypothyroidism:

  a) 10 mg in 70 mL of corn syrup once daily. Monitor T_4 levels one week after initiation of therapy. Obtain one blood sample just before administration and on sample 2–3 hours after dosing. (Chen and Li 1987)

  For adjunctive treatment of equine metabolic syndrome to lower the risk for laminitis:

  a) 48 mg (total dose) in the feed once daily for 3–6 months. When discontinuing treatment, wean off the drug by reducing dose to 24 mg a day for 2 weeks, then 12 mg a day for 2 weeks. The benefits of longer treatment at lower dosages of levothyroxine have not been evaluated. (Frank 2007)

- **BIRDS:**

  For hypothyroidism:

  a) One 0.1 mg tablet in 30 mL–120 mL of water daily; stir water and offer for 15 minutes and remove. Use high dose for budgerigars and low dose for water drinkers. Used for respiratory clicking, vomiting in budgerigars and thyroid responsive problems. (Clubb 1986)

- **REPTILES:**

  For hypothyroidism in tortoises:

  a) 0.02 mg/kg PO every other day (Gauvin 1993)

Monitoring

- Therapeutic efficacy should be judged first via clinical effects, and, if necessary serum T4
- Serum T_4; after therapy is started wait at a week before measuring T_4. Draw level preferably just prior to the next dose. Dosage should generally be reduced if serum thyroxine levels exceed 100 ng/mL or signs of thyrotoxicosis develop.

Client Information

- Clients should be instructed in the importance of compliance with therapy as prescribed.
- Also, review the signs that can be seen with too much thyroid supplementation (see Overdosage section above).

Chemistry/Synonyms

Prepared synthetically for commercial use, levothyroxine sodium is the levo isomer of thyroxine that is the primary secretion of the thyroid gland. It occurs as an odorless, light yellow to buff-colored, tasteless, hygroscopic powder that is very slightly soluble in water and slightly soluble in alcohol. The commercially available powders for injection also contain mannitol.

100 micrograms of levothyroxine is approximately equivalent to 65 mg (1 grain) of desiccated thyroid.

Levothyroxine sodium may also be known as: T_4, T_4 thyroxine sodium, levothyroxin natrium, levothyroxinum natricum, 3,5,3',5'-tetra-iodo-L-thyronine sodium, thyroxine sodium, L-thyroxine sodium, thyroxinum natricum, tirossina, and tiroxina sodica; many trade names are available.

Storage/Stability/Compatibility

Levothyroxine sodium preparations should be stored at room temperature in tight, light-resistant containers. The injectable product should be reconstituted immediately before use; unused injection should be discarded after reconstituting. Do not mix levothyroxine sodium injection with other drugs or IV fluids.

Levothyroxine sodium is reportedly unstable in aqueous solutions. If using a commercial liquid preparation, it is suggested to obtain validated stability data for the product.

Dosage Forms/Regulatory Status

All levothyroxine products require a prescription, but are not necessarily FDA approved. There have been bioavailability differences between products reported. It is recommended to use a reputable product and not to change brands indiscriminately.

VETERINARY-LABELED PRODUCTS:

Levothyroxine Sodium Tablets: 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg, (1 mg *Soloxine®*); *Amtech® Levothyroxine Sodium Tablets* (IVX); *Levosyn®* (V.E.T.); *Soloxine®* (Virbac); *Thyro-Tabs®* (Vet-A-Mix); *Thyrosyn®* (Vedco); *Thyroxine-L Tablets®* (Butler); *Thyrozine®* (Phoenix Pharmaceutical); *Thyrokare® Tablets* (Neogen); (Rx). Labeled for use in dogs.

Levothyroxine Sodium Tablets Chewable (Veterinary) 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg; *Canine Thyroid Chewable Tablets®* (Pala-Tech); *Nutrived® T-4 Chewable Tablets* (Vedco); *Heska Thyromed® Chewable Tablets* (Heska); (Rx). Labeled for use in dogs.

Levothyroxine Oral Solution: 1 mg/mL in 30 mL bottles: *Leventa® Oral Solution* (Intervet); (Rx) Labeled for use in dogs.

Levothyroxine Sodium Powder (Veterinary): 0.22% (1 gram of T_4 in 454 grams of powder): One level teaspoonful contains 12 mg of T_4. Available in 1 lb. and 10 lb. containers; *Equine Thyroid Supplement®* (Pala-Tech); *Thyrozine Powder®* (Phoenix Pharmaceutical); *Levoxine® Powder* (First Priority); *Thyro-L®* (Vet-A-Mix); *Throxine-L® Powder* (Butler); *Equi-Phar Thyrosyn Powder®* (Vedco); *Thyrokare® Powder* (Neogen); (Rx). Labeled for use in horses.

HUMAN-LABELED PRODUCTS:

Levothyroxine Sodium Tablets: 0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.1 mg, 0.112 mg, 0.125 mg, 0.137 mg, 0.15 mg, 0.175 mg, 0.2 mg & 0.3 mg; *Synthroid®* (Abbott); *Levothroid®* (Forest); *Levoxyl®* (Jones Pharma); *Thyro-Tabs®* (Lloyd); *Unithroid®* (Lannett); generic; (Rx)

Levothyroxine Powder for Injection lyophilized: 200 micrograms & 500 micrograms in 10 mL vials; generic; (Rx)

LIDOCAINE HCL (SYSTEMIC)

(*lye*-doe-kane) Xylocaine®

ANTIARRHYTHMIC/LOCAL ANESTHETIC

Prescriber Highlights

- Local anesthetic & antiarrhythmic agent; may be useful to prevent post-operative ileus, reperfusion injury in horses
- Contraindications: Known hypersensitivity to the amide-class local anesthetics, severe degree of SA, AV, or intraventricular heart block (if not being artificially paced), or Adams-Stokes syndrome
- Caution: Liver disease, congestive heart failure, shock, hypovolemia, severe respiratory depression, marked hypoxia, bradycardia, or incomplete heart block having VPC's, unless the heart rate is first accelerated
- Cats might be more sensitive to the CNS effects of lidocaine; use with caution
- Patients susceptible to malignant hyperthermia should receive intensified monitoring
- Adverse Effects: Most common adverse effects reported are dose related (serum level) & mild. CNS signs include drowsiness, depression, ataxia, muscle tremors, etc.; nausea & vomiting (usually transient). Adverse cardiac effects usually only at high plasma concentrations
- When an IV bolus is given too rapidly, hypotension may occur
- Do NOT use the product containing epinephrine intravenously
- Drug interactions

Uses/Indications

Besides its use as a local and topical anesthetic agent, lidocaine is used to treat ventricular arrhythmias, principally ventricular tachycardia and ventricular premature complexes in all species. Cats may be more sensitive to the drug and some clinicians feel that it should not be used in this species as an antiarrhythmic, but this remains controversial. In horses, lidocaine may be useful to prevent post-operative ileus and reperfusion injury.

Pharmacology/Actions

Lidocaine is considered to be a class IB (membrane-stabilizing) antidysrhythmic agent. It is thought that lidocaine acts by combining with fast sodium channels when inactive which inhibits recovery after repolarization. Class IB agents demonstrate rapid rates of attachment and dissociation to sodium channels. At therapeutic levels, lidocaine causes phase 4 diastolic depolarization attenuation, decreased automaticity, and either a decrease or no change in membrane responsiveness and excitability. These effects will occur at serum levels that will not inhibit the automaticity of the SA node, and will have little effect on AV node conduction or His-Purkinje conduction.

Lidocaine apparently has some enhancing effects on intestinal motility in patients with postoperative ileus. The mechanism for this effect is not well understood, but probably involves more than just blocking increased sympathetic tone.

Lidocaine has been shown to be a scavenger of reactive oxygen species (ROS) and lipid peroxidation