METHIMAZOLE (Veterinary—Systemic)

Another commonly used generic name for this medication is thiamazole. A commonly used *brand name* for a human-labeled product is *Tapazole*.

Category: Antihyperthyroid agent.

Indications

Note: Methimazole is not specifically approved for veterinary use. In other USP information monographs, the [EL]US and [EL]CAN designations refer to uses that are not included in U.S. and Canadian product labeling; however, in this monograph they reflect the lack of veterinary products and, therefore, product labeling.

Classification as *Accepted, Potentially effective,* or *Unaccepted* is an evaluation of reasonable use that considers clinical circumstances, including the availability of other therapies. The quality of evidence reviewed for an indication is shown by the evidence rating.

Cats

Accepted

[EL]US,CAN Hyperthyroidism (treatment)[EL]—Methimazole tablets are used in the treatment of hyperthyroidism in cats (Evidence rating: A-2,3,4).{R-1-5} Methimazole may be used for short-term management when practical considerations delay radioiodine treatment or to reduce the risk of complications from thyroid surgery. Alternatively, it may used as the only treatment to control hyperthyroidism.

Because it is a reversible treatment, methimazole can be useful in assessing whether the reduced glomerular filtration rate that occurs in the transition from hyperthyroidism to a euthyroid state will lead to significant renal decompensation in cats with renal disease.{R-6}

Potentially effective

[EL]US,CAN Hyperthyroidism (treatment)[EL]—Although the efficacy of methimazole compounded in a pluronic lecithin organogel (PLO) dosage form has not been established, it may be used in the treatment of hyperthyroidism in cats when other therapies are impractical (Evidence rating: B-2,3,4).{R-7-10} The only pharmacokinetic study available showed poor to no bioavailability for methimazole formulated in PLO and administered as a single dose inside the pinna of healthy cats.{R-10} Because multiple-dose pharmacokinetic studies have not been performed to document, if present, adequate and consistent drug absorption over time, the current basis for use of transdermal gel in selected cases are studies reporting clinical response and reduction of serum thyroxine in hyperthyroid cats when administered methimazole in a transdermal formulation daily for 4 weeks.{R-7-9} Potential concerns with this dosage form are slower response to treatment and less reliable reduction of serum thyroxine to within euthyroid range than is seen with oral methimazole administration.{R-8}

Regulatory Considerations

U.S. and Canada—

There are no commercial veterinary methimazole products. There are methimazole tablets labeled for human use but there is no commercial topical gel for systemic delivery. If methimazole transdermal gel is prescribed, it must be compounded for veterinary use. At this time, there is no consistent, accepted formula for compounding pluronic lecithin organogel or other transdermal formulations; therefore, the strength, purity, quality, and stability of this dosage form may vary from pharmacy to pharmacy. In the United States, refer to the Animal Medicinal Drug Use Clarification Act, Food and Drug Administration regulations pertaining to compounding (CFR 21 Part 530.13), and the current Food and Drug Administration's Compliance Policy Guide on *Compounding of Drugs for Use in Animals.*{R-11-13} In Canada, refer to the Health Canada Health Products and Food Branch's *Policy on Manufacturing and Compounding Drug Products in Canada* (POL-0051).{R-14}

Evidence ratings

Evidence Quality	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Insufficient evidence to support a recommendation for use
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use

Evidence Type	
1	Species-specific evidence from at least one large randomized and controlled trial (RCT) or multiple small RCTs
2	Species-specific evidence from a small RCT, disease models, large case studies, pharmacokinetic studies using surrogate endpoints, or evidence from well-designed trials in a different species that is considered appropriate for comparison
3	Dramatic results from either well-designed, species-specific trials without controls or small case studies
4	Pharmacokinetic studies without surrogate endpoints
5	*In vitro* studies
6	Opinions of respected authorities on the basis of clinical experience or reports of expert committees

Chemistry

Chemical group: Thioimidazole derivative.[R-15]

Chemical Name: 2*H*-Imidazole-2-thione, 1,3-dihydro-1-methyl-.[R-16]

Molecular formula: $C_4H_6N_2S$.[R-16]

Molecular weight: 114.17.[R-16]

Description: Methimazole USP—White to pale buff, crystalline powder, having a faint, characteristic odor. Its solutions are practically neutral to litmus.[R-17]

Solubility: Methimazole USP—Freely soluble in water, in alcohol, and in chloroform; slightly soluble in ether.[R-17]

Pharmacology/Pharmacokinetics

Mechanism of action/Effect: Methimazole inhibits thyroid peroxidase, which catalyzes the oxidation of iodide to liberate iodine for incorporation into tyrosine residues on thyroglobulin for the formation of thyroxine (T_4) and triiodothyronine (T_3).[R-18; 39]

Methimazole has no effect on existing thyroid hormones already circulating or stored in the thyroid gland and doesn't inhibit the peripheral conversion of T_4 to T_3.[R-18; 19; 39] Therefore, it generally takes 2 to 4 weeks for serum T_4 to reach the normal range in hyperthyroid cats treated with methimazole.

Transdermal vehicle: Pluronic lecithin oranogels (PLOs) are described as enhancing drug absorption across the stratum corneum but the mechanism of action and effectiveness in cats has not been clearly demonstrated.[R-9]

Other effects: Some experimental evidence suggests the administration of a high dose of methimazole (40 mg per kg of body weight) shortly before treatment with certain nephrotoxic medications, such as cisplatin, may provide some protection against renal damage.[R-27-32] Because methimazole does not prevent the uptake of nephrotoxins by the kidney, it has been theorized that protection is provided by an antioxidant effect; however, further study is needed to confirm this theory.[R-27; 29; 32] It is not suggested that hyperthyroid cats would be protected against nephrotoxins with therapeutic dosing; methimazole overdosage in these cats, already at risk for renal disease, is not recommended.

Absorption:

Oral—Methimazole is considered to be quickly and well absorbed with oral administration.

Oral absolute bioavailability (F relative to intravenous administration):

Cats, healthy—81.1 ± 11.4% (range, 27 to 100%);[R-3] 75.6 ± 9.2%;[R-4] 40.4 ± 8.1%.[R-10]

Cats, hyperthyroid—79.5 ± 4.9%.[R-4]

Transdermal—Although the efficacy studies cited in this monograph imply that methimazole is absorbed systemically with multiple-dose treatment, at this time there are no pharmacokinetic data documenting effective absorption of any drug in a PLO gel when administered to cats.

Absorption of methimazole in PLO was shown to be highly variable in cats given a single 5-mg dose. Only 2 of 6 cats achieved detectable serum methimazole.[R-10]

Transdermal absolute bioavailability (F relative to intravenous administration): *Cats,* healthy—11.4 ± 18.7%.[R-10]

Distribution: Steady state volume of distribution (Vd_{ss})—

Cats, healthy: 0.80 ± 0.07 liter per kilogram (L/kg);[R-3] 0.83 ± 0.12 L/kg;[R-4] 0.89 ± 0.42 L/kg.[R-10] After two weeks of treatment, Vd_{ss} was significantly decreased to 0.66 ± 0.05 L/kg.[R-3]

Cats, hyperthyroid: 0.66 ± 0.58 L/kg. In this study, the authors found no statistically significant difference in Vd_{ss} between normal cats and hyperthyroid cats.[R-4]

Dogs: 0.590 ± 0.121 L/kg.[R-27]

Biotransformation:

Human beings—Primarily hepatic.[R-39]

Cats—Unknown.[R-39]

Duration of action: The efficacy of methimazole is believed to be largely determined by intrathyroidal concentration rather than serum concentration; however, residence time in the feline thyroid gland has not been studied and dosage is adjusted based on total serum T_4 concentration.[R-43]

After twelve cats were given long-term oral methimazole therapy to bring serum T_4 concentrations to within the normal range, methimazole was discontinued; within 2 days, serum T_4 in all cats was back into the hyperthyroid range.[R-5]

Mean residence time in the body—*Cats:* 5.06 ± 0.69 hours, after a single total oral dose of 5 mg per cat.[R-26]

Human data—In human patients, the serum half-life of methimazole is 4 to 6 hours but it appears to be resident in the human thyroid gland for at least 20 hours.[R-5; 40]

Half-life: Elimination—

With intravenous administration:

Cats, healthy—6.6 ± 2.0 hours (range, 1.9 to 15.1 hours);[R-3] 4.7 ± 1.4 hours;[R-4] 4.5 ± 2.6 hours.[R-10] There was no significant change in half-life after 2 weeks of oral methimazole administration, when a half-life of 3.4 ± 0.2 hours was measured; however, values became less variable among cats (range, 2.3 to 4.0 hours).[R-3]

Cats, hyperthyroid—2.3 ± 0.4 hours. In this study, the authors found no significant difference in elimination half-life between normal cats and hyperthyroid cats..[R-4]

Dogs—8.82 ± 1.33 hours.[R-27]

With oral administration of a single total dose of 5 mg per cat: *Cats,* healthy—4.45 ± 1.04 hours.[R-26]

Concentrations: *Cats*—Peak serum concentration (C_{max}) and time to peak (T_{max}) with a single total dose of 5 mg per cat:

Oral administration—1.84 ± 0.19 micrograms per mL (mcg/mL) at 1.19 ± 0.42 hours after administration.[R-4; 26]

Transdermal administration—0.05 ± 0.09 mcg/mL (mean of 6 cats).[R-10] Peak concentrations were 0 mcg/mL in all but 2 cats; in these cats the peaks, 0.07 and 0.25 mcg/mL, occurred at 7.6 and 1.9 hours, respectively.[R-10]

Elimination: Route of elimination in cats is unknown.

Clearance—

Cats, healthy: 2.2 ± 0.6 milliliter per minute per kilogram (mL/min/kg);[R-3] 2.9 ± 0.38 mL/min/kg;[R-4] 3.0 ± 1.2 mL/min/kg.[R-10] No significant difference was found in clearance after two weeks of methimazole administration.[R-3]

Cats, hyperthyroid: 4.0 ± 0.4 mL/min/kg. In this study, the authors found no significant difference in clearance between normal cats and hyperthyroid cats.[R-4]

Dogs: 0.814 ± 0.123 mL/min/kg.[R-27]

Precautions to Consider

Reproduction/Pregnancy

Methimazole has the potential to create significant neurodevelopmental problems by causing hypothyroidism in mother and fetus. Effects could include cognitive dysfunction in the offspring, some consequences of which are not reversible with thyroid hormone therapy.[R-43]

Human beings: Methimazole crosses the placenta and can cause goiter or cretinism in a developing fetus. Potential congenital defects include aplasia cutis, esophageal atresia with tracheoesophageal fistula, or choanal atresia.[R-19]

Lactation

Human beings: Methimazole is distributed into milk in lactating mothers.[R-19]

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Medications that undergo liver microsomal oxidation, including:

Albendazole

Fenbendazole

Oxfendazole

(Pharmacokinetic studies have demonstrated inhibition of the hepatic metabolism of benzimidazoles when administered to mice and sheep concurrently with methimazole. The clinical impact of the resulting prolonged residence of active intermediate metabolites is unknown.)[R-33-35]

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance):

With diagnostic test values

Antinuclear antibodies (ANA) and

Direct antiglobulin test (DAT)

(A positive ANA test has been reported in significant numbers of cats during high-dose methimazole treatment [10 to 15 mg a day]; however, disease states have not been reported in association with this response. The effect may be duration- and dose-dependent, developing with long-term therapy but resolving in some cats when the dose is reduced.)[R-5]

Thyroid scintigraphy

(Based on a study in hyperthyroid cats, concurrent methimazole treatment does not affect results of diagnostic pertechnetate [$^{99m}TcO_4$] thyroid scans)[R-22]

(An artifact of reduced thyroxine and possibly increased thyroid-stimulating hormone [TSH], in cats treated with too high a dose of methimazole, is a stimulation of normal or less active tissue to take up $^{99m}TcO_4$. This effect may have been the

cause of enhanced uptake of $^{99m}TcO_4$ by the thyroid gland in a study of normal cats during the period after ending methimazole treatment. It may also be an explanation for the findings in a study of hyperthyroid cats, in which areas of the thyroid that appeared normal in pretreatment tests began taking up $^{99m}TcO_4$ while the cats were receiving methimazole.)[R-22; 23 43]

With physiology/laboratory test values
- Eosinophilia and
- Leukopenia and
- Lymphocytosis
  - (Mild hematologic changes that may occur have been reported to be transient, even with ongoing methimazole treatment; see also *Side/Adverse Effects* in this monograph for information on more serious dyscrasias)[R-5]
- Blood urea nitrogen (BUN) and
- Creatinine, serum
  - (Because of reduced glomerular filtration rate [GFR] in the transition from hyperthyroid to euthyroid status, cats may show a mild to significant increase in BUN and/or creatinine.)[R-6; 8; 20]

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance).

Except under special circumstances, this medication should not be used when the following medical problems exist:
- Hypersensitivity to methimazole[R-39; 43]
  - (A previous severe reaction to methimazole or sensitivity to other thioureylenes, such as propylthiouracil or carbimazole, makes treatment contraindicated.)

Risk-benefit should be considered when the following medical problems exist:
- Autoimmune disease or
- Hematologic abnormalities or
- Hepatic disease
  - (Methimazole is reported to cause hepatopathy, blood dyscrasias, and altered antinuclear antibody or direct antiglobulin test results in some cats and may aggravate already existing disease.)
- Renal dysfunction, pre-existing[R-6; 20]
  - (Hyperthyroid cats have a higher glomerular filtration rate [GFR] than normal cats and conversion to a euthyroid state typically decreases GFR to a more normal level. An elevation in blood urea nitrogen [BUN] can occur in cats with this transition. A few cats may develop clinical signs of renal disease with treatment for hyperthyroidism; cats with overt renal disease may worsen. Careful initial dosing and monitoring of T_4 concentration is recommended to insure iatrogenic hypothyroidism does not aggravate renal stress that may already be present. Because hyperthyroidism and the associated glomerular hyperfiltration may aggravate renal disease over time, treatment of hyperthyroidism is desirable if significant decompensation does not develop.)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; » = major clinical significance):
- Alanine aminotransferase (ALT [SGPT]) values, serum and
- Alkaline phosphatase values, serum and
- Bilirubin, total
  - (A small number of cats have developed hepatotoxicity during oral or transdermal methimazole treatment.)[R-5; 8]
- Blood urea nitrogen (BUN) concentrations and
- Creatinine concentrations, serum
  - (Renal tests are particularly important in the first 30 days of treatment to monitor the effect of reduced GFR. In addition, many hyperthyroid cats are older and may have an elevated risk of renal dysfunction over time.)[R-6; 20]
- Complete blood count (CBC) and
- Platelet count
  - (Periodic CBCs with platelet counts are done to monitor for potential adverse effects; the greatest risk may be in the first 3 months.)[R-21]
  - (If methimazole is given to stabilize a cat prior to surgery, a platelet count is performed in preparation for surgery.)
- Serum thyroxine (T_4) concentration
  - (Periodic samples are tested to monitor therapeutic efficacy. Samples can be drawn at any time during the day.)[R-21]

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:

Those indicating need for medical attention

Incidence more frequent

Cats
- ***Anorexia and/or vomiting***—especially with oral administration; ***lethargy; mild hematologic***

abnormalities, including eosinophilia, lymphocytosis, and leukopenia[R-2; 5]

Note: *Gastrointestinal signs* have been reported in as many as 23% of closely-monitored cats administered recommended dosages (5 mg a day).[R-2] One large retrospective reported an incidence of 11% and resolution of signs in many cats without ending treatment; however, some persistently vomited while on oral methimazole.[R-5]

Gastrointestinal effects appear to be less common in cats administered transdermal methimazole than those given oral methimazole.[R-8]

Mild hematologic abnormalities may occur in up to 11% of cats and appear to be generally self-limiting during treatment; however, more serious blood dyscrasias require discontinuation of therapy (see below).[R-5]

Incidence less frequent or unknown

Cats

Agranulocytosis, thrombocytopenia (in some cases, epistaxis, oral hemorrhage), ***or pancytopenia;***[R-5; 7; 21; 36] ***bleeding without thrombocytopenia;***[R-5; 21] ***enlarged lymph nodes;***[R-38] ***facial and/or cervical excoriation;***[R-2; 5] ***hepatopathy*** (anorexia, icterus, lethargy, vomiting);[R-2; 5; 7] ***local cutaneous reaction***—with topical administration;[R-7] ***myasthenia gravis, acquired***[R-18]

Note: In one study compiling up to 262 cases given 10 to 15 mg of methimazole a day, the above effects occurred in ≤ 3% of cats.[R-5]

Agranulocytosis, thrombocyopenia, facial and/or cervical excoriations, and *hepatopathy* may resolve once therapy is ended. Although clinical improvement in hepatopathy often occurs quickly, resolution of laboratory alterations and jaundice required 45 days in one cat.[R-5]

Facial excoriations seen in association with oral administration are reported to be fairly unresponsive to anti-inflammatory therapy; 2 to 15% of cats treated have been reported to develop this effect.[R-2; 5] A *local cutaneous reaction* seen in association with transdermal administration in one clinical study appeared to be clinically different from the facial excoriations seen with oral administration.[R-7] It is not known how many cats may suffer local reactions with long-term transdermal administration.

Myasthenia gravis is considered a rare effect, with 4 reported cases in cats after 2 to 4 months of treatment. Signs stopped with discontinuation of methimazole or with the addition of prednisolone administration to treatment.[R-42]

Overdose

For more information in cases of overdose or unintentional ingestion, **contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center** (888-426-4435 or 900-443-0000; a fee may be required for consultation) **and/or the drug manufacturer**.

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:

Note: Toxicity studies are not available for cats.[R-39]

Dogs

With an intravenous dose of 40 mg/kg:

Vomiting—occurred in 1 of 5 dogs given a single high dose[R-27]

Human beings[R-19]

Agranulocytosis or pancytopenia (generally associated with doses of 40 mg/kg or more); ***central nervous system stimulation or depression; edema; exfoliative dermatitis; fever; hepatitis; joint pain; nephrotic syndrome; neuropathies; pruritis; vomiting***

Treatment of toxicity

Treatment recommended by the manufacturer in human product labeling consists of the following:[R-19]

- Administering activated charcoal may reduce absorption of methimazole and speed elimination.
- Support airway ventilation and cardiovascular perfusion
- Monitor bone marrow function
- If thyroxine (T_4) falls to very low concentrations, signs (lethargy, muscular weakness) can be reversed by administration of levothyroxine at replacement dosage.[R-43]

Client Consultation

In providing consultation, consider emphasizing the following selected information:

Familiarizing clients with signs of adverse effects, including bleeding, dermatitis, jaundice, or continuing gastrointestinal signs, and instructing them to contact their veterinarian when signs are observed

With transdermal gel, instructions on how to administer (see dosage instructions below in this monograph). Instructions to call the veterinarian and/or pharmacist if the gel separates or appears

nonhomogenous

General Dosing Information

Establishing therapeutic dose

Cats: Oral administration—Serum thyroxine (T_4) is typically tested 2 to 3 and then 4 to 6 weeks after initiation of treatment, with significant decreases expected within 2 to 4 weeks. Blood urea nitrogen (BUN) and serum creatinine are performed at the same time, as it may be useful to coordinate renal response to thyroxine concentration to adjust the dosage in renal decompensation.{R-42} Complete blood count (CBC), platelet count, serum alkaline phosphatase (SAP), and serum alanine aminotransferase (ALT) are also performed during the initial phase (1 to 3 months) of treatment. All tests may be repeated if the cat becomes ill.{R-42} Timing of subsequent tests is based on response to treatment and the necessity of adjusting dosage to the lowest that is effective.{R-39}

Transdermal administration—In addition to the testing recommended for oral administration, additional T_4 monitoring is performed periodically to insure the dosage form is still effective.

Diet

Oral absorption does not appear to be significantly affected by administration with a small amount of food.{R-3}

Dosing and Dosage Forms

Note: Methimazole is not specifically approved for veterinary use. In other USP information monographs the ELUS and ELCAN designations indicate uses that are not included in U.S. and Canadian product labeling; however, in this section they reflect the lack of veterinary products and, therefore, product labeling.

DOSAGES

ELUS,CAN***Cats***—

For *Methimazole Tablets USP*

Hyperthyroidism: Oral, initial *total* dose of 2.5 mg *per cat* every twelve hours for cats with mild to moderate hyperthyroidism.{R-2} For cats with more severe disease, or that are not euthyroid within two to four weeks with the initial dose, a dose of 5 mg per cat every twelve hours, or, in some cases, every eight hours, may be used.{R-1; 2} In rare cases, 10 mg per cat every twelve hours may be necessary. The dosage is adjusted to the lowest needed to maintain the euthyroid state. Some cats can eventually be maintained with 10 to 15 mg as a single total daily dose.{R-41} Cats that develop gastrointestinal side effects during the initial treatment phase may respond to dividing the total daily dose to be given every eight hours.

For *Methimazole Transdermal Gel, Veterinary*

Note: Hyperthyroidism—Although the safety and efficacy have not been established, a topical dose of 2.5 to 5 mg as a *total* dose *per cat* every twelve hours has been used.{R-7; 8} Residue from the previous treatment on the ear should be gently removed with a moistened cotton ball. The administrator should wear gloves and alternate treatment from the inner surface of one pinna to another with each dose.EL

Be aware that this dosage is based on limited studies performed with a pluronic lecithin oranogel (PLO) formulation. There is no accepted, consistent formula for compounding PLO formulations. The strength, purity, quality, and stability of PLO products may vary from pharmacy to pharmacy. In addition, transdermal vehicles other than PLO, for which there are no studies of bioavailablility or efficacy, are available through compounding pharmacies but cannot be recommended without further study.

The pluronic portion of PLO gel is thermoreversible, making it liquid at lower temperatures, such as refrigeration, and gel at higher temperatures, such as room or body temperature. Pluronic liquification and separation of the transdermal gel so that it appears nonhomogenous may occur under conditions like refrigeration. Gel that has separated may not deliver a consistent dose and should not be used.

DOSAGE FORMS

Oral

METHIMAZOLE TABLETS USP

Strength(s) usually available:

U.S.—

Human-labeled product(s):{R-19}

5 mg (Rx) [*Tapazole;* GENERIC].

10 mg (Rx) [*Tapazole;* GENERIC].

Canada—

Human-labeled product(s):

5 mg (Rx) [*Tapazole;* GENERIC].

Caution: Keep out of the reach of children.

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a well-closed and light-resistant container, unless otherwise specified by the manufacturer.

USP requirements: Preserve in well-closed, light-resistant containers. Contain the labeled amount, within ± 6%. Meet the requirements for Identification, Dissolution (80% in 30 minutes in water in Apparatus 1 at 100 rpm), and Uniformity of dosage units.{R-17}

Topical

METHIMAZOLE TRANSDERMAL GEL, VETERINARY

Strength(s) usually available: Methimazole transdermal gel is not available as a commercial product in the United States or Canada. Therefore, it must be compounded for veterinary use. Research studies used a transdermal formulation in pluronic lecithin organogel (PLO) with a methimazole concentration of 50 mg per mL (5 mg per 0.1 mL). Utilizing the services of a qualified compounding pharmacist to formulate this dosage form is recommended.

Caution: Keep out of the reach of children.

Packaging and storage: Pending.

USP requirements: Proposal pending.

Developed: 02/04/08

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Oral methimazole for the treatment of hyperthyroidism in cats.

Revision date: July 11, 2007

Back to the indication

The following tables are not intended to be in-depth reviews of each article. Instead, they are brief overviews/reviews of the studies, assuming reviewers are already familiar with the cited references. If you would like additional information about these studies, please contact veterinary@usp.org.

Study 1 of 6: Milner RJ, Channell CD, Levy JK, et. al. Survival times for cats with hyperthyroidism treated with iodine 131, methimazole, or both: 167 cases (1996-2003). Journal of the American Veterinary Medicine Association 2006; 228 (4): 559-63.

Design	**Goal:** To compare the effects of type of therapy and other factors on survival times.	**Limitations:**
• Retrospective study N = 167	**Methods:** • Medical records of cats at the University of Florida Veterinary Medical Center; hyperthyroidism had been confirmed by high serum thyroxine (T_4) concentration, by the results of thyroid scintigraphy, or by both tests between 1996 and 2003. • Methimazole vs radioiodine therapy vs methimazole and radioiodine **Dose:** • Methimazole dosage ranged from 2.5 mg to 10 mg total dose per cat a day - Methimazole-only therapy was given for the life of the cat. - If followed by ^{131}I, methimazole therapy lasted a median of 88 days. **Results:** • 55 (33%) of 166 cats were treated with ^{131}I alone, 65 (39%) were treated with methimazole followed by ^{131}I, and 47 (28%) were treated with methimazole alone. • Twenty-four (14%) cats had preexisting renal disease, and 115 (69%) had preexisting hepatic disease. Cats with preexisting renal disease had significantly shorter survival times than did cats without preexisting renal disease ($P = 0.023$). • Age was positively correlated ($r = 0.4$, $P < 0.01$) with survival time, with older cats more likely to live longer; however, the authors interpreted this cautiously as 4 of the 10 cats in the 4- to 9-year-old age group were eliminated from analysis because they were still alive at the time the study ended, and 3 of the 10 had severe cardiac disease before the study. • When cats with preexisting renal disease were excluded, median survival time for cats treated with methimazole alone (2.0 years; interquartile range [IQR], 1 to 3.9 years) was significantly shorter than median survival time for cats treated with ^{131}I alone (4.0 years; IQR, 3.0 to 4.8 years) or methimazole followed by ^{131}I (5.3 years; IQR, 2.2 to 6.5 years). **Conclusions:** • Cats being treated with methimazole alone had significantly shorter survival times than cats treated with ^{131}I or methimazole followed by ^{131}I.	• Most cats were older cats (median, 15.1 years). • Accuracy of medical records was a concern. • Potential bias in case selection

Study 2 of 6: Trepanier LA, Hoffman SB, Kroll M, et al. Efficacy and safety of once versus twice daily administration of methimazole in cats with hyperthyroidism. Journal of the American Veterinary Medical Association 2003; 222(7): 954-8.

Design	**Goal:** To investigate whether once daily administration of methimazole is as safe and effective as twice daily administration in cats with hyperthyroidism.	**Limitations:**
• Open, randomized, dosage-response controlled clinical trial N = 40	**Methods:** • A complete physical examination, including measurement of body weight; complete blood count (CBC); serum biochemical analyses, including measurement of serum thyroxine (T_4) concentration; urinalysis; and blood pressure measurement were done before treatment, 2 weeks after, and 4 weeks after initiation of treatment. Diagnosis was based on T_4 and clinical signs. **Dose:** • Group 1: Oral, 5 mg of methimazole every 24 hours (N = 25) • Group 2: Oral, 2.5 mg of methimazole every 12 hours (N =15) **Results:** • Serum thyroxine concentration was significantly higher in cats given methimazole once daily, compared with cats given methimazole twice daily. Concentrations for each group were 3.7 vs 2.0 mcg/dL at 2 weeks and 3.2 vs 1.7 mcg/dL at 4 weeks, respectively, after initiation of treatment. • After 2 weeks of treatment, the percentage of euthyroid cats in the group receiving methimazole once a day (54%) was significantly lower (P = 0.04) than in the group receiving methimazole twice a day (87%). After 4 weeks of treatment, euthyroid cats in the group receiving methimazole once a day (71%) was still lower than in the group receiving methimazole twice a day (92%); although there was no longer a significant difference (P = 0.17) in percentage. • The percentage of cats with adverse effects (42% overall, primarily gastrointestinal tract upset and facial excoriation) was not significantly different between groups (P = 0.25). **Conclusions:** • Results suggest that administration of 5 mg of methimazole once a day was not as effective as administration of 2.5 mg twice a day and cannot be recommended for routine use.	• Did not investigate administration of a higher dose (10 mg daily)

Study 3 of 6: Becker TJ, Graves TK, Kruger JM, et al. Effects of methimazole on renal function in cats with hyperthyroidism. Journal of the American Animal Hospital Association 2000 May-Jun; 36(3): 215-23.

Design • Prospective, open, cohort study N = 12 cats with naturally occuring hyperthy-roidism and 20 clinically normal cats	**Goal:** To investigate the effects of methimazole on renal function in cats with and without hyperthyroidism. **Methods:** • All cats initially were evaluated with a history, physical examination, complete blood count, serum biochemistry profile, basal serum total thyroxine concentration, complete urinalysis, and urine bacterial culture. Glomerular filtration rate (GFR) was estimated by a plasma iohexol clearance (PIC) test. Mean age of hyperthyroid cats was 12.5 ± 2.9 years; normal cats were aged 11.8 ± 2.0 years. • After initial evaluation, hyperthyroid cats (Group 1) were treated with methimazole until euthyroidism was achieved, based on serum T_4 performed every two weeks. **Dose:** • Group 1: Hyperthyroid cats were given 5 mg of oral methimazole every twelve hours. The dose was adjusted, based on serum T_4, until euthyroidism was reached. • Group 2: Clinically normal cats were given no treatment. **Duration:** • The initial tests were repeated for both groups four to six weeks later. **Results:** • The mean pretreatment estimated GFR for the hyperthyroid cats was significantly higher (3.83 ± 1.82 mL/kg/min) than that of the control cats (1.83 ± 0.56 mL/kg/min). Control of hyperthyroidism resulted in a significant drop in mean GFR to 2.02 ± 0.81 mL/kg/min, which was a comparable value to the normal cats at that time (2.05 ± 0.30 mL/kg/min). • Although the hyperthyroid cats as a group did not have statistically significant increases in mean serum urea nitrogen and creatinine concentrations or decreases in mean urine specific gravity after treatment, when compared to pretreatment values, 2 of the 12 cats developed abnormally high serum creatinine concentrations. Methimazole treatment was discontinued in these two cats and tests for renal function (SUN and creatinine) improved. • Treatment was also discontinued in one cat that developed hemolytic anemia. **Conclusions:** • These hyperthyroid cats had increased GFR compared to normal cats, and treatment with methimazole resulted in a decrease in GFR to that found in clinically healthy cats. • It may be useful to treat hyperthyroid cats with methimazole initially, to ascertain whether overt renal failure will occur when the cat is euthyroid. • Additional studies are needed to determine the effect of long-term, untreated hyperthyrodism on renal function.	

Study 4 of 6: Trepanier LA, Peterson ME, Aucoin DP. Pharmacokinetics of intravenous and oral methimazole following single- and multiple-dose administration in normal cats. Journal of Veterinary Pharmacology and Therapeutics 1991 Dec; 14(4): 367-73.

Design		**Limitations:**
• Pharmaco-kinetic study N = 6 clinically normal cats	**Goal:** To record the pharmacokinetics of methimazole administered to cats as single and multiple doses. **Methods:** • Young adult domestic shorthaired cats with normal serum T_4. Healthy, based on clinical exam, CBC, and serum biochemistry. **Dose:** Single dose study— • Day 1: Intravenous, 5 mg total dose per cat • Day 2: Oral, 5 mg total dose per cat Multiple dose study— • Day 2: A second oral dose was apparently given twelve hours after the first oral dose on Day 2, beginning the multidose study. • Day 3: Oral, 5 mg total dose per cat every twelve hours, continued for a total of 14 days • Twelve hours after the last oral dose: Intravenous, 5 mg total dose per cat **Results:** • Oral administration, single dose—Methimazole was rapidly and well absorbed when administered orally, with food. Oral bioavailability = 81.1 ± 11.4%. Peak serum concentration (C_{max}) = 1.7 ± 0.2 mcg/mL at 1.2 ± 0.4 hour. • Intravenous administration— Single dose: Elimination half-life ($T_{1/2}$) = 6.6 ± 2.0 hours, with a wide range of values (1.9 h to 15.1 h) Clearance (Cl) = 2.2 ± 0.6 mL/min/kg Volume of distribution (Vd_{ss}) = 0.8 ± 0.1 L/kg Multiple dose (single intravenous dose after 2 weeks of oral administration): No statistically significant change in mean serum concentration, $T_{1/2}$, or Cl was found after multiple-dose administration. After two weeks of treatment, Vd_{ss} was significantly decreased to 0.66 ± 0.05 L/kg. • Two cats with the longest baseline $T_{1/2}$ (9.9 h and 15.1 h), however, did exhibit markedly shorter $T_{1/2}$ (3.5 h and 3.3 h, respectively) after multiple-dose administration. Values for central and steady state volumes of distribution also decreased after multiple-dose administration, possibly indicating saturation of thyroid uptake of methimazole with chronic administration. **Conclusions:** • Results indicate that methimazole has good oral bioavailability and a longer serum elimination half-life than propylthiouracil.	• A longer duration study is needed to determine whether individual cats can develop drug-induced acceleration of metabolism.

Study 5 of 6: Trepanier LA, Peterson ME, Aucoin DP. Pharmacokinetics of methimazole in normal cats and in cats with hyperthyroidism. Research in Veterinary Science 1991 Jan; 50(1): 69-74.

<table>
<tr>
<td>Design
• Pharmaco-kinetic study

N = 10 clinically normal cats, 9 hyperthy-roid cats</td>
<td>Goal: To investigate the disposition of methimazole after intravenous and oral administration to clinically normal cats and cats with naturally occurring hyperthyroidism

Methods:
• Normal cats were 2 to 6 years of age and healthy, based on exam, T_4, feline leukemia and feline immunodeficiency virus tests, CBC, and biochemistry.
• Hyperthyroid cats were 10 to 18 years of age with diagnosis based on history, clinical signs, and elevated T_4.

Dose:
• Day 1—Intravenous, 5 mg as a single total dose per cat
• Day 2—Oral, 5 mg as a single total dose per cat

Results:
• With oral administration, the mean bioavailability of methimazole was high in both the normal cats (77.6 %) and cats with hyperthyroidism (79.5 %). There were no significant differences in C_{max} or T_{max} between normal and hyperthyroid cats.
• After intravenous or oral administration, the mean residence time (MRT) was significantly shorter ($P < 0.05$) in the cats with hyperthyroidism (oral, 3.4 hours) than in the normal cats (5.4 hours).
• In general, values for all parameters were much less variable in hyperthyroid cats than in normal cats.

<table>
<tr><th>Hyperthyroid cats</th><th>Normal cats</th></tr>
<tr><td>IV administration</td><td>IV administration</td></tr>
<tr><td>$T_{1/2}$ = 2.3 ± 0.4 hours
Cl = 4.0 ± 0.4 mL/min/kg
Vd_{ss} = 0.664 ± 0.058 L/kg</td><td>$T_{1/2}$ = 4.7 ± 1.4 hours
Cl = 2.9 ± 0.4 mL/min/kg
Vd_{ss} = 0.826 ± 0.116 L/kg</td></tr>
<tr><td>Oral administration</td><td>Oral administration</td></tr>
<tr><td>C_{max} = 1.6 ± 0.2 mcg/mL
T_{max} = 0.8 ± 0.2 hours
$T_{1/2}$ = 2.5 ± 0.3 hours</td><td>C_{max} = 1.9 ± 0.2 mcg/mL
T_{max} = 1.1 ± 0.4 hours
$T_{1/2}$ = 5.1 ± 1.1 hours</td></tr>
</table>
Conclusions:
• Methimazole appears to have good oral bioavailability.
• With the exception of faster elimination, most pharmacokinetic parameters for methimazole were not altered by the hyperthyroid state.</td>
<td>Limitations:
• No data are available on the rate of elimination of methimazole from the thyroid gland in cats.</td>
</tr>
</table>

Study 6 of 6: Peterson ME, Kintzer PP, Hurvitz AI. Methimazole treatment of 262 cats with hyperthyroidism. Journal of Veterinary Internal Medicine 1988; 2: 150-7.

Design • Open, uncontrol-led clinical trial N = 262	**Goal:** To investigate the efficacy and safety of methimazole in the treatment of feline hyperthyroidism **Methods:** • The Animal Medical Center, Cornell University, New York from June 1983 to June 1986. Average age of cats was 13.5 ± 2.5 years. Diagnosis was based on clinical signs and serum T_4. • Methimazole was administered to 181 cats for 7 to 130 days (mean, 27.7 days) in preparation for thyroidectomy. • Methimazole was administered to 81 cats as the only therapy for hyperthyroidism for 30 to 1,000 days (mean, 228 days). **Dose:** • Oral, 10 to 15 mg a day, divided into two to three doses. **Results:** • After 2 to 3 weeks of methimazole therapy, mean serum thyroxine (T_4) concentration decreased significantly ($P < 0.001$), from a pretreatment value of 12.1 micrograms per decaliter (mcg/dL) to 2.1 mcg/dL. • The dose was adjusted based on a target T_4 range of 0.8 to 2.5 microgram per decaliter (mcg/dL). The lowest dose needed to maintain euthyroidism in the 81 cats that were given methimazole as sole treatment for hyperthyroidism ranged from 2.5 to 20 mg per day (mean, 11.9 mg per day). • Clinical side effects developed in 48 (18.3%) cats, usually within the first month of therapy. Effects included anorexia, vomiting, lethargy, self-induced excoriation of the face and neck, bleeding diathesis, and icterus caused by hepatopathy. Mild hematologic abnormalities, including eosinophilia, lymphocytosis, and slight leukopenia, developed in 43 (16.4%) cats, usually within the first 2 months of treatment. In ten (3.8%) cats, more serious hematologic reactions developed, including agranulocytosis and thrombocytopenia. Serious hematologic abnormalities resolved within 1 week after cessation of methimazole treatment. Immunologic abnormalities associated with methimazole treatment included the development of antinuclear antibodies in 52 of 238 (21.8%) cats tested and red cell autoantibodies, as evidenced by positive direct antiglobulin tests, in 3 cats of 160 tested (1.6%). **Conclusions:** • Results suggest that methimazole is safe and effective in the treatment of feline hyperthyroidism.	

Transdermal methimazole for the treatment of hyperthyroidism in cats.

Revision date: July 11, 2007

Back to the indication

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Study 1 of 4: Lecuyer M, Prini S, Dunn ME, et al. Clinical efficacy and safety of transdermal methimazole in the treatment of feline hyperthyroidism. Canadian Veteterinary Journal 2006 Feb; 47: 131-5.

Design		**Limitations:**
• Open, uncontrol-led trial N = 10	**Goal:** To investigate whether methimazole, delivered by the transdermal route, is an effective and safe treatment for hyperthyroidism **Methods:** • Cats, newly diagnosed with hyperthyroidism at University of Montreal Centre Hospitalier Universitaire Veterinarie, based on ≥ 2 of 3 criteria: clinical signs, a palpated thyroid nodule, serum total thyroxine (T_4) >55 nanomole/liter (nmol/L). • Physical exam and baseline hematologic and biochemical values, along with serum thyroxine (T_4) levels, were performed on presentation (D0), evaluation at 14 days (D14) and 28 days (D28) following initiation of therapy. • Statistical analysis performed using Number Cruncher Statistical System (NCCS 2001). Reponse to therapy evaluated by Kruskal-Wallis one-way ANOVA. **Dose:** • Formulation is methimazole in pleurolecithin oranogel (PLO) from a compounding laboratory. • Topical, 5 mg (0.1 mL of gel) applied to the internal ear pinna every twelve hours for twenty-eight days. Treatments were to be applied to alternate ears, and residue from previous treatments to be removed by the owner before application. **Results:** • 13 cats were enrolled. One cat was withdrawn due to severe facial erythema of the internal pinnae and thrombocytopenia Two cats were euthanized after the 14th day. No gastrointestinal side effects were seen. • Clinical improvement, as well as a significant decrease in T_4, was noted in all cats. However, only two owners elected to use the gel for long-term treatment. • Mean serum T_4 measured at D0 was 97.31 ± 37.55 nmol/L, at D14 was 27.44 ± 37.51 nmol/L, and at D28 was 14.63 ± 10.65 nmol/L (reference range, 19 to 45 nmol/L). Values at D14 and D28 were significantly decreased (P < 0.0001) compared to values at D0. **Conclusions:** • Results suggest that transdermal methimazole is effective and safe, but should not be a first choice treatment.	• One-third of owners reported the gel was not homogenous. Although they were requested to mix it before administration, the delivered dose may have varied daily due to formulation separation. Long-term formulation stability studies should be performed. • Pharmacokine-tic data for transdermal methimazole was not collected.

Study 2 of 4: Sartor LL, Trepanier LA, Kroll MM, et al. Efficacy and safety of transdermal methimazole in the treatment of cats with hyperthyroidism. Journal of Veterinary Internal Medicine 2004; 18: 651-5.

Design	**Goal:** To investigate whether transdermal methimazole is as safe and effective as oral methimazole for the control of hyperthyroidism in cats.	**Limitations:**
• Randomized, route of administration-response controlled clinical trial N = 44	**Methods:** • Cats with newly diagnosed hyperthyroidism were randomized to receive either transdermal methimazole in pluronic lecithin organogel (PLO, 50 mg/mL; applied to the inner pinna) or oral methimazole. • Cats were evaluated before treatment and at weeks 2 and 4 by physical exam, body weight, complete blood count, biochemical panel, urinalysis, total serum levothyroxine (T_4) concentration, indirect Doppler blood pressure determination, and completion of an owner questionnaire. • Data between the 2 groups and over time were compared by nonparametric methods. **Dose:** • Group 1 (27 cats): Topical, 2.5 mg as a total dose per cat every twelve hours for four weeks • Group 2 (17 cats): Oral, 2.5 mg as a total dose per cat every twelve hours for four weeks **Results:** • 44 cats completed the protocol. 3 cats were withdrawn because: 1) owner elected radioiodine treatment 2) lymphoma diagnosis 3) euthanasia • Significantly more cats treated with oral methimazole had serum T_4 concentrations within the reference range after 2 weeks (14 of 16 cats) compared to those treated by the transdermal route (14 of 25; P = .027). This difference was no longer significant by 4 weeks of treatment (9 of 11 for oral versus 14 of 21 for transdermal). • Cats treated with oral methimazole had a higher incidence of gastrointestinal (GI) adverse effects (4 of 17 cats) compared to the cats treated with transdermal methimazole (1 of 27; P = .04), but no differences were found between groups in the incidence of neutropenia, hepatotoxicity, or facial excoriations. **Conclusions:** • Although the overall efficacy of transdermal methimazole is not as high as that of oral methimazole at 2 weeks of treatment, it is a safe and effective therapy for feline hyperthyroidism and is associated with fewer GI adverse effects compared to the oral route.	• Because fewer cats entered the oral treatment group, there were not enough subjects at 4 weeks to document a statistical difference between groups.

Study 3 of 4: Hoffmann G, Marks SL, Taboada J, et al. Transdermal methimazole treatment in cats with hyperthyroidism. Journal of Feline Medicine and Surgery. 2003 Apr; 5(2): 77-82.

Design	**Goal:** To investigate, in hyperthyroid cats, serum thyroxine concentration and clinical response to treatment with transdermal methimazole, and to determine if further investigation is indicated	**Limitations:**
• Retrospec-tive study N = 13	**Methods:** • Clinical and laboratory data for 13 cats from eight veterinary hospitals using a laboratory in Baton Rouge, LA. Diagnosis made by clinical signs and thyroxine concentrations. Mean age was 13.7 years. • Treatment was with methimazole (Tapazole, Eli Lilly), formulated in a PLO-based vehicle (50 mg/mL) and applied to the inner pinna of the ear. Medications were stored at room temperature. • Cats were re-evaluated for the first time at a mean of 4.3 weeks, and again at a mean of 5.4 months after treatment began. Eight cats returned for the second follow-up. **Dose:** • Topical, 2.5 to 20 mg as a total daily dose, in some cases divided into a dose every twelve hours. **Results:** • Clinical improvement was observed in all cats. • No adverse effects were noted. Cats previously vomiting in association with oral methimazole, showed no gastrointestinal signs with transdermal administration. • Total serum T_4 at the first recheck was within normal range in 7 of 10 cats presented and was decreased in 2 cats. Cats that were not euthyroid were receiving $\leq$ 7.5 mg a day. • Total serum T_4 at the second recheck was within normal range in 7 of 8 cats presented. The cat that was not euthyroid was receiving 7.5 mg total dose a day. **Conclusions:** • Transdermally administered methimazole resulted in decrease of serum T_4 in hyperthyroid cats with no adverse effects. Further investigation is warranted.	• Although cats were followed for several months with no recorded adverse effects, longer term studies are needed.

Study 4 of 4: Hoffman SB, Yoder AR, Trepanier LA. Bioavailability of transdermal methimazole in a pluronic lecithin organogel (PLO) in healthy cats. Journal of Veterinary Pharmacology and Therapeutics 2002; 25: 189-93.

Design	**Goal:** To investigate bioavailability, relative to i.v. and oral routes of administration, of transdermal methimazole in a PLO gel in cats.	**Limitations:**
• Pharmaco-kinetic study N = 6	**Methods:** • Young, healthy, adult domestic shorthair cats were randomly assigned to receive 5 mg of methimazole by the intravenous (IV), oral (PO), or transdermal routes, in a triple crossover protocol with 1 week washout between doses. • Blood samples were taken for high performance liquid chromatography (HPLC) determination of serum methimazole, at 0, 5, 15, 30, 60 min, and 2, 4, 6, 12, and 24 hours after dosing. **Dose:** • Oral, intravenous, or topical, 5 mg as a total single dose per cat **Results:** • Methimazole absorption following topical administration was poor and variable, with only two of six cats achieving detectable serum methimazole concentrations at any time point following transdermal administration. • With transdermal administration, area under the concentration-time curve (AUC), maximum concentration (C_{max}), and absolute bioavailability were all significantly lower (0.39 ± 0.63 microgram hour/milliliter [mcg h/mL], 0.05 ± 0.09 mcg/mL, and 11.4 ± 18.7%, respectively) than for either intravenous (7.96 ± 4.38 mcg h/mL, 3.34 ± 2.00 mcg/mL, 100%) or oral routes (2.94 ± 1.24 mcg h/mL, 0.51 ± 0.15 mcg/mL, 40.4 ± 8.1%). **Conclusions:** • Results indicate generally low to undetectable bioavailability of methimazole in PLO given as a single transdermal dose to healthy cats. • One individual cat did achieve a relative bioavailability of transdermal to oral administration nearing 100% (absolute bioavailability of 51%). • The results are inconsistent with a recent retrospective study showing 7 of 10 hyperthyroid cats becoming euthyroid within 4 weeks of starting transdermal methimazole. Further study of this dosage form is warranted to determine bioavailability after multiple doses.	• Pharmacokinetic studies in diseased cats would be useful.