Chemistry/Synonyms

Methenamine is chemically unrelated to other anti-infective agents. It is commercially available in two salts, methenamine mandelate and methenamine hippurate. Methenamine mandelate occurs as a white, crystalline powder and contains approximately 48% methenamine and 52% mandelic acid. It is very soluble in water. Methenamine hippurate occurs as a white, crystalline powder with a sour taste and contains approximately 44% methenamine and 56% hippuric acid. It is freely soluble in water.

Methenamine may also be known as: hexamine amygdalate, hexamine mandelate, mandelato de metenamina, *Aci-steril®*, *Hiprex®*, *Mandelamine®*, *Reflux®*, *Urocedulamin®*, and *Urex®*.

Storage/Stability/Compatibility

Commercially available methenamine products should be stored at room temperature. Because acids hydrolyze methenamine to formaldehyde and ammonia, do not mix with acidic vehicles before administering. Methenamine is physically **incompatible** when mixed with most alkaloids and metallic salts (*e.g.*, ferric, mercuric or silver salts). Ammonium salts or alkalis will darken methenamine.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Methenamine Mandelate Tablets: 0.5 gram & 1 gram; enteric-coated: 0.5 g & 1 g; *Mandelamine®* (Warner Chilcott); generic; (Rx)

Methenamine Mandelate Suspension: 0.5 g/5mL in 480 mL; generic; (Rx)

Methenamine Hippurate Tablets: 1 gram; *Hiprex®* (Hoechst Marion Roussel); *Urex®* (3M Pharm); (Rx)

METHIMAZOLE

(meth-***im***-a-zole) Tapazole®

Prescriber Highlights

- Used for medical treatment of feline hyperthyroidism
- Potentially, transdermal gels with methimazole may have efficacy in cats (or owners) that cannot tolerate oral dosing
- Contraindications: Hypersensitivity to it
- Caution: History of or concurrent hematologic abnormalities, liver disease, or autoimmune disease
- Adverse Effects: Most occur within first 3 mos. of treatment: vomiting, anorexia, & depression most frequent. Eosinophilia, leukopenia, & lymphocytosis are usually transient. Rare, but serious: self-induced excoriations, bleeding, hepatopathy, thrombocytopenia, agranulocytosis, positive direct antiglobulin test, & acquired myasthenia gravis
- Place kittens on milk replacer if mother receiving drug
- Very bitter taste

Uses/Indications

Methimazole is considered by most clinicians to be the agent of choice when using drugs to treat feline hyperthyroidism. Propylthiouracil has significantly higher incidences of adverse reactions when compared to methimazole and is rarely used today. Transdermal methimazole (in PLO gel; 2.5 mg twice daily) has been used with some therapeutic success in cats that do not tolerate oral dosing. Efficacy may require four or more weeks to detect. Studies are ongoing.

Methimazole appears to be useful for the prophylactic prevention of cisplatin induced nephrotoxicity in dogs.

Pharmacology/Actions

Methimazole interferes with iodine incorporation into tyrosyl residues of thyroglobulin, thereby inhibiting the synthesis of thyroid hormones. It also inhibits iodinated tyrosyl residues from coupling to form iodothyronine. Methimazole has no effect on the release or activity of thyroid hormones already formed or in the general circulation.

Pharmacokinetics

Information on the pharmacokinetics of methimazole in cats is available (Trepanier, Peterson, and Aucoin 1989). These researchers reported that in normal cats, the bioavailability of the drug is highly variable (45–98%), as is the volume of distribution (0.12–0.84 L/kg). After oral dosing, plasma elimination half-life ranges from 2.3–10.2 hours. There is usually a 1–3 week lag time between starting the drug and significant reductions in serum T_4. In dogs, methimazole has a serum half-life of 8–9 hours. Methimazole apparently concentrates in thyroid tissue.

Contraindications/Precautions/Warnings

Methimazole is contraindicated in patients who are hypersensitive to it. It should be used very cautiously in patients with a history of or concurrent hematologic abnormalities, liver disease, or autoimmune disease.

Adverse Effects

Most adverse effects associated with methimazole use in cats occur within the first three months of therapy, with vomiting, anorexia, and depression/lethargy occurring most frequently. GI effects occur in about 10% of treated cats may be related to the drug's bitter taste or direct gastric irritation and are usually transient. Eosinophilia, leukopenia, thrombocytopenia, and lymphocytosis may be noted in approximately 15% of cats treated within the first 8 weeks of therapy. These hematologic effects usually are also transient and generally do not require drug withdrawal. Other more serious but rare adverse effects include: self-induced facial excoriations (2.3%), bleeding (2.3%), hepatopathy (1.5%), thrombocytopenia (2.7%), agranulocytosis (1.5%), and positive direct antiglobulin test (1.9%). These effects generally require withdrawal of the drug and adjunctive therapy. Up to 50% of cats receiving methimazole chronically (>6 months) will develop a positive ANA, requiring dosage reduction. Rarely cats will develop an acquired myasthenia gravis that requires either withdrawal or concomitant glucocorticoid therapy.

Reproductive/Nursing Safety

High levels of methimazole cross the placenta and may induce hypothyroidism in kittens born of queens receiving the drug. In humans, the FDA categorizes this drug as category ***D*** for use during pregnancy (*There is evidence of human fetal risk, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.*)

Levels higher than those found in plasma are detected in human breast milk. It is suggested that kittens be placed on a milk replacer after receiving colostrum from mothers on methimazole.

Overdosage/Acute Toxicity

Acute toxicity that may be seen with overdosage include those that are listed above under Adverse Effects. Agranulocytosis, hepatopathy, and thrombocytopenias are perhaps the most serious effects

that may be seen. Treatment consists of following standard protocols in handling an oral ingestion (empty stomach, if not contraindicated, administer charcoal, etc.) and to treat symptomatically and supportively.

Drug Interactions

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

- **BUPROPION**: Potential for increased risk for hepatotoxicity; increased monitoring (LFT's) necessary
- **DIGOXIN**: Methimazole may decrease digoxin efficacy
- **WARFARIN**: Potential for decreased anticoagulant efficacy if methimazole added

Doses

- **DOGS:**

  As an investigative method to reduce nephrotoxicity associated with cisplatin therapy:

  a) 40 mg/kg IV over one minute prior to cisplatin. (Kitchell and Dhaliwal 2000) **Note:** No commercially available parenteral product in USA at time of writing.

- **CATS:**

  For hyperthyroidism:

  a) For cats with azotemia or for clients declining radioiodine: 1.25–5 mg per cat twice daily (start at lower end. (Trepanier 2007)

  b) Initially, 2.5 mg (total dose) PO once a day for 2 weeks. If adverse reactions not noted by owner, physical exam reveals no new problems, CBC and platelets are within normal limits, and serum T4 concentration is greater than 26 nmol/L after 2 weeks of therapy, the dose is increased to 2.5 mg PO twice daily and the same parameters are checked in another 2 weeks. The dosage should then be increased every 2 weeks by 2.5 mg per day until serum T4 is between 13 and 26 nmol/L or adverse effects develop. Serum T4 concentrations decline into the reference range within 1–2 weeks, once the cat is receiving an effective dose. (Nelson 2003b)

  c) If no signs of renal insufficiency/failure, begin at 5 mg (total dose) PO twice daily in cases with severely increased T4 levels. If renal insufficiency present (or not sure), start at 2.5 mg twice daily. If azotemia and overt renal failure, start at 1.25 mg twice a day. Monitor in 1–2 weeks (T4, CBC with platelet count, renal blood parameters, urinalysis). Monitor for other signs of adverse effects. Based on clinical signs and bloodwork, dose can be increased slowly. Monitor every 2–3 weeks for the first 3 months, then every 3–6 months thereafter. (Ward 2003)

  d) 5 mg two to three times a day. Goal is to maintain T4 in the low or low normal range. Recheck serum T4, CBC with platelets and chemistry panel at 2–3 week intervals. After first 3 months may recheck less frequently. (Taboada 2000)

  e) Methimazole (50 mg/mL; 5 mg/0.1 mL) in PLO for *transdermal administration:* 2.5 mg to inner pinna q12h. Person applying should wear gloves or finger cots. Somewhat lower efficacy than PO (67% vs 82% euthyroid at 4 weeks). Lower incidence of GI effects with transdermal (4% vs. 24%). No difference in facial excoriation, neutropenia, hepatotoxicity, or thrombocytopenia. Drawbacks for transdermal include: erythema at application site, increased cost, and stability of compounded med (2 weeks guaranteed stable). (Trepanier 2006)

Monitoring

During first 3 months of therapy (baseline values and every 2–3 weeks):

- CBC, platelet count
- Serum T_4
- If indicated by symptomatology: liver function tests, ANA

After stabilized (at least 3 months of therapy):

- T_4 at 3–6 month intervals
- Other diagnostic tests as dictated by adverse effects

Client Information

- It must be stressed to owners that this drug will decrease excessive thyroid hormones, but does not cure the condition and that compliance with the treatment regimen is necessary for success.

Chemistry/Synonyms

A thioimidazole-derivative antithyroid drug, methimazole occurs as a white to pale buff crystalline powder, having a faint characteristic odor and a melting point of 144–147°C. It is freely soluble (1 gram in 5 mL) in water or alcohol.

Methimazole may also be known as: thiamazole, mercazolylum, methylmercaptoimidazole, thiamazolum; tiamazol, *Antitiroide®*, *Danantizol®*, *Favistan®*, *Mercaptizol®*, *Metibasol®*, *Strumazol®*, *Tapazol®*, *Thacapzol®*, *Thycapzol®*, *Thyrozol®*, *Tirodril®*, and *Unimazole®*.

Storage/Stability

Methimazole tablets should be stored in well-closed, light-resistant containers at room temperature.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Methimazole Tablets (plain & scored): 5 mg & 10 mg; *Tapazole®* (Monarch); generic; (Par Pharm); (Rx)

METHIONINE
DL-METHIONINE
RACEMETHIONINE

(me-*thye*-oh-neen) Ammonil®

URINARY ACIDIFIER; NUTRITIONAL

Prescriber Highlights

- **Used primarily as a urinary acidifier; questionable efficacy in reducing stone formation**
- **Contraindications: Renal failure, pancreatic disease, hepatic insufficiency, preexisting acidosis, or urate calculi; not recommended for kittens**
- **Adverse Effects: Gastrointestinal distress (food may alleviate), Heinz-body hemolytic anemia (cats)**
- **Drug interactions**