

## **PRODUCT MONOGRAPH**

**Pr TAPAZOLE®**

Methimazole Tablets, USP  
5, 10 and 20 mg

**Antithyroid Agent**

**PALADIN LABS INC.**  
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## Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY OF PRODUCT INFORMATION .....	3
INDICATIONS AND CLINICAL USE.....	3
CONTRAINDICATIONS .....	3
WARNINGS AND PRECAUTIONS.....	4
ADVERSE REACTIONS.....	6
DRUG INTERACTIONS .....	6
OVERDOSAGE .....	7
STORAGE AND STABILITY.....	8
DOSAGE FORMS, COMPOSITION AND PACKAGING .....	9
PART II: SCIENTIFIC INFORMATION .....	10
PHARMACEUTICAL INFORMATION.....	10
PART III: CONSUMER INFORMATION.....	11

**Pr TAPAZOLE®**

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**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY OF PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Non-medicinal Ingredients</b>
Oral	Tablet 5, 10 and 20 mg	Lactose monohydrate <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

**INDICATIONS AND CLINICAL USE**

- Tapazole® (methimazole) is indicated in the medical treatment of hyperthyroidism. Long-term therapy may lead to remission of the disease.
- Tapazole® may be used to ameliorate hyperthyroidism in preparation for subtotal thyroidectomy or radioactive iodine therapy.
- Tapazole® is also used when thyroidectomy is contraindicated or not advisable.

**CONTRAINDICATIONS**

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the *Dosage Forms, Composition and Packaging* section of the product monograph.
- Nursing mothers, as the drug is excreted in breast milk.

## WARNINGS AND PRECAUTIONS

### Serious Warning and Precautions

Agranulocytosis (see **Hematologic** section below)

Liver toxicity (see **Hepatic/Biliary/Pancreatic** section below)

### **General**

Patients who receive methimazole should be under close surveillance. Physicians should encourage patients to immediately report any evidence of illness or unusual clinical symptoms, particularly sore throat, skin eruptions, fever, headache or general malaise. In such cases, white blood cell and differential counts should be made to determine whether agranulocytosis has developed. Particular care should be exercised with patients who are receiving additional drugs known to cause agranulocytosis.

The development of arthralgias should prompt drug discontinuation, since this symptom may indicate a severe transient migratory polyarthritis known as “the antithyroid arthritis syndrome”.

### **Carcinogenesis and Mutagenesis**

Rats treated for 2 years with methimazole demonstrated thyroid hyperplasia and thyroid adenoma and carcinoma formation. Such findings are seen with continuous suppression of thyroid function by sufficient doses of a variety of antithyroid agents. Pituitary adenomas have also been observed.

### **Endocrine and Metabolism**

#### **Lactose**

Tapazole tablets contain lactose monohydrate. Patients with hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this product.

### **Hematologic**

Agranulocytosis is potentially the most serious side effect of therapy with methimazole. Patients should be instructed to report to their physicians any symptoms of agranulocytosis, such as fever or sore throat. Leukopenia, thrombocytopenia, and aplastic anemia (pancytopenia) may also occur. The drug should be discontinued in the presence of agranulocytosis or plastic anemia (pancytopenia). The patient’s bone marrow function should be monitored. **See Monitoring and Laboratory Tests.**

### **Anticoagulant Therapy**

Treating patients with both methimazole and warfarin necessitates intensive and frequent

monitoring, in particular when initiating, discontinuing or changing doses of methimazole, since alterations in the thyroid function affect the response to anticoagulation. **See Drug-Drug Interactions.**

### **Hepatic/Biliary/Pancreatic**

Due to the similar hepatic toxicity profiles of methimazole and propylthiouracil, attention is drawn to the severe hepatic reactions, which have occurred with both drugs. There have been rare reports of fulminant hepatitis, hepatic necrosis, encephalopathy and death. Cholestatic jaundice has occurred rarely. Patients should be instructed to report symptoms of hepatic dysfunction such as jaundice, anorexia, pruritus, and/or right upper-quadrant pain. Their presence should prompt evaluation of liver function tests and discontinuation of methimazole. Drug treatment should be discontinued promptly in the event of clinically significant evidence of liver abnormality, including hepatic transaminase values exceeding 3 times the upper limit of normal. **See Monitoring and Laboratory Tests.**

### **Skin**

The drug should be discontinued in the presence of exfoliative dermatitis.

### **Special Populations**

**Pregnant Women:** Methimazole can cause fetal harm when administered to a pregnant woman. Methimazole readily crosses the placental membranes and can induce goiter and even cretinism in the developing fetus. In addition, rare instances of aplasia cutis, as manifested by scalp defects have occurred in infants born to mothers who received methimazole during pregnancy. If methimazole is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be warned of the potential hazard to the fetus.

Since scalp defects have not been reported in offspring of patients treated with propylthiouracil, this agent may be preferable to methimazole in pregnant women requiring treatment with antithyroid drugs.

Methimazole used judiciously is an effective drug in the treatment of hyperthyroidism complicated by pregnancy. In many pregnant women, the thyroid dysfunction diminishes as the pregnancy proceeds; consequently, a reduction in dosage may be possible. In some instances, use of methimazole can be discontinued 2 or 3 weeks before delivery.

**Nursing Women:** Methimazole is excreted in human breast milk and its use is contraindicated in nursing mothers.

**Pediatrics:** No formal studies have been conducted in the pediatric population.

**Geriatrics:** No formal studies have been conducted in the geriatric population.

## **Monitoring and Laboratory Tests**

The patient's liver function, hepatic transaminase levels, and the complete blood count should be closely monitored. See **Boxed Warning** and **Hematologic** section above. Because methimazole may cause hypoprothrombinemia and bleeding, prothrombin time/INR should also be monitored during therapy with the drug, especially before surgical procedures.

Periodic monitoring of thyroid function is warranted. A laboratory result indicating elevated TSH warrants a decrease in the dosage of methimazole.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

Adverse reactions occur in less than 1 percent of patients.

Serious adverse reactions (which occur less frequently than the minor less serious adverse reactions) include inhibition of myelopoiesis (agranulocytosis, granulocytopenia and thrombocytopenia), aplastic anemia, drug fever, a lupus-like syndrome, insulin autoimmune syndrome (which can result in hypoglycemic coma), hepatitis (jaundice may persist for several weeks after discontinuation of the drug), periarteritis and hypoprothrombinemia. Nephritis occurs very rarely. Cholestatic jaundice, fulminant hepatitis, encephalopathy, hepatic necrosis and death have been rarely reported. (see **Warning and precautions** section)

Less serious adverse reactions include skin rash, urticaria, nausea, vomiting, epigastric distress, arthralgia, paresthesia, loss of taste, abnormal loss of hair, myalgia, headache, pruritus, drowsiness, neuritis, edema, vertigo, skin pigmentation, jaundice, sialadenopathy, anorexia, right upper-quadrant pain and lymphadenopathy.

### **Abnormal Hematologic and Clinical Chemistry Findings**

It should be noted that about 10% of patients with untreated hyperthyroidism have leucopenia (white-blood-cell count of less than 4,000/mm<sup>3</sup>), often with relative granulopenia.

## **DRUG INTERACTIONS**

### **Drug-Drug Interactions:**

Increases and decreases in warfarin-induced anticoagulation have been reported in patients taking methimazole. In hyperthyroid patients, the metabolism of vitamin K clotting factors is increased, resulting in increased sensitivity to oral anticoagulants. Antithyroid drugs, by reducing the extent of hyperthyroidism, decrease the metabolism of clotting factors and thus reduce the effects of oral anticoagulants. On the other hand, patients on anticoagulant therapy who are euthyroid due to antithyroid agents may develop marked hypoprothrombinemia if the antithyroid medications are ceased and they become thyrotoxic again. Treating patients with both methimazole and warfarin necessitates intensive and frequent monitoring, in particular

when initiating, discontinuing or changing doses of methimazole, since alterations in thyroid function affect the response to anticoagulation.

### **Drug-Food Interactions**

Interactions with foods have not been studied.

### **Drug-Herb Interactions**

Interactions with herbal products have not been studied.

### **Drug-Laboratory Test Interactions**

Interactions with laboratory tests have not been studied.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

- Methimazole is administered orally.
- It is usually given in three equal doses a day at approximately eight-hour intervals.

### **Recommended Dose and Dosage Adjustment**

**Adult:** The initial daily dose is 15 mg for mild hyperthyroidism, 30 to 40 mg for moderately severe hyperthyroidism and 60 mg for severe hyperthyroidism, divided into three doses at eight-hour intervals. The maintenance dosage is 5 to 15 mg daily.

**Pediatric:** Initially, the daily dosage is 0.4 mg/kg of body weight divided into three doses and given at eight-hour intervals. The maintenance dosage is approximately ½ of the initial dose.

### **Missed Dose**

No data is available.

## **OVERDOSAGE**

For management of suspected drug overdose, contact your regional Poison Control Centre.
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**Symptoms:** Symptoms may include nausea, vomiting, epigastric distress, headache, fever, joint pain, pruritus and edema. Aplastic anemia (pancytopenia) or agranulocytosis may be manifested in hours to days. Less frequent events are hepatitis, nephrotic syndrome, exfoliative dermatitis, neuropathies and CNS stimulation or depression. Although not well studied, methimazole-induced agranulocytosis is generally associated with doses of 40 mg or more in patients older than 40 years of age.

No information is available on the median lethal dose of the drug or the concentration of methimazole in biologic fluids associated with toxicity and/or death.

**Treatment:** In managing overdose, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. The patient's bone marrow function should be monitored. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Forced diuresis, peritoneal dialysis, hemodialysis or charcoal hemoperfusion have not been established as beneficial for an overdose of methimazole.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

Methimazole inhibits the synthesis of thyroid hormones and thus is effective in the treatment of hyperthyroidism. The drug does not inactivate existing thyroxine and triiodo-thyroxine that are stored in the thyroid or circulating in the blood, nor does it interfere with the effectiveness of thyroid hormones given by mouth or by injection.

The actions and use of methimazole are similar to those of propylthiouracil. On a weight basis, the drug is at least ten times as potent as propylthiouracil, but methimazole may be less consistent in action.

### **Pharmacokinetics**

**Absorption:** Methimazole is readily absorbed from the gastrointestinal tract.

**Metabolism:** It is metabolized rapidly and requires frequent administration.

**Excretion:** Methimazole is excreted in the urine.

## **STORAGE AND STABILITY**

Store at room temperature (15 to 30 °C). Protect from light. Keep tightly closed.



## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

### Tapazole<sup>®</sup> 5 mg tablets:

- Each round, white, scored tablet is debossed with 'J94' on one side and plain on the other side.
- Each tablet contains 5 mg methimazole.
- Available in bottles of 100.

### Tapazole<sup>®</sup> 10 mg tablets:

- Each round, white tablet is debossed with '10' on one side and plain on the other side.
- Each tablet contains 10 mg methimazole.
- Available in bottles of 100.

### Tapazole<sup>®</sup> 20 mg tablets:

- Each round, white tablet is debossed with '20' on one side and plain on the other side.
- Each tablet contains 20 mg methimazole.
- Available in bottles of 100.

Non-medicinal ingredients: Corn starch, lactose monohydrate, magnesium stearate, talc

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

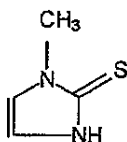
#### Drug Substance

Proper name: Methimazole

Chemical name: 1-Methylimidazole-2-thiol

Molecular formula and molecular mass:  $C_4H_6N_2S$   
114.16 g / mol

Structural formula:



Physicochemical properties:

**Description:**

White to slightly cream-coloured crystalline powder. It differs chemically from the drugs of the thiouracil series primarily because it has a five- instead of a six-membered ring.

**Melting range:**

143 - 146°C

**Solubility:**

Freely soluble in water, alcohol and in acetone

#### CLINICAL TRIALS

No data is available.

#### DETAILED PHARMACOLOGY

No data is available.

#### TOXICOLOGY

No data is available.

## PART III: CONSUMER INFORMATION

### Tapazole® Methimazole Tablets, USP

This leaflet is part III of a three-part "Product Monograph" published when Tapazole® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Tapazole®. Contact your doctor or pharmacist if you have any questions about the drug.

#### ABOUT THIS MEDICATION

##### What the medication is used for:

- Tapazole® is used in the treatment of hyperthyroidism (overactive thyroid gland).
- Tapazole® is used for treating and preparing the overactive thyroid gland for surgical removal or for radioactive iodine treatment.
- Tapazole® is also used when the overactive thyroid gland cannot be removed.

##### What it does:

- Tapazole® inhibits the synthesis (production) of thyroid hormones.
- The drug does not affect the levels of the thyroid hormones that are already present in the thyroid gland or are circulating in the blood.

##### When it should not be used:

- If you are hypersensitive (allergic) to methimazole or any of the ingredients in Tapazole®.
- If you are breastfeeding.

##### What the medicinal ingredient is:

Methimazole

##### What the important nonmedicinal ingredients are:

Corn starch, lactose monohydrate, magnesium stearate, talc

##### What dosage form it comes in:

5, 10, and 20 mg tablets.

#### WARNINGS AND PRECAUTIONS

##### Serious Warnings and Precautions

##### Possible serious side effects include:

- agranulocytosis (a marked decrease in white blood cell counts)
- liver toxicity

##### **BEFORE you use Tapazole® talk to your doctor or pharmacist if:**

- you have a low white blood cell count
- you have joint pain. Tapazole® may result in antithyroid arthritis syndrome
- you have liver disease
- you have a skin disease
- you are intolerant to milk sugar. Tapazole® contains a milk sugar (lactose).
- you are pregnant or planning to become pregnant
- you are breast feeding or planning to breast feed

#### INTERACTIONS WITH THIS MEDICATION

**Drugs that may interact with Tapazole® include:** anticoagulants (blood thinning drugs)

Talk to your doctor or pharmacist if you are taking any other medicine, prescription or non-prescription.

#### PROPER USE OF THIS MEDICATION

You should follow the dose and directions given by your doctor.

Tapazole® daily dose should be divided into the three equal doses, taken orally every 8 hours.

##### **Usual Adult dose:**

Initial daily dose:

15 mg for mild hyperthyroidism

30 mg to 40 mg for moderately severe hyperthyroidism

60 mg for severe hyperthyroidism

Maintenance daily dose: 5 mg to 15 mg

**Usual children dose:**

Initial daily dose: 0.4 mg/kg of body weight  
 Maintenance daily dose: approximately ½ the initial dose.

**Overdose:**

Symptoms may include nausea, vomiting, stomach discomfort, headache, fever, joint pain, rash and edema (fluid retention or swelling).

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed dose:**

Talk to your doctor or pharmacist if you miss one of your scheduled doses of Tapazole®.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Common side effects are:

- skin rash, hives (urticaria), itching, skin pigmentation
- nausea, vomiting, heart burn, loss of taste, anorexia (eating disorder)
- joint pain, muscle pain, numbness
- hair loss
- headache, drowsiness, dizziness
- neuritis (inflammation of a nerve, often with pain or tenderness), edema (swelling due to fluid build up)
- a disease of the lymph node (sialadenopathy and lymphadenopathy)

If you notice any side effects not mentioned above, or any above-mentioned side effects persist or become bothersome, please contact your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	If effect persists or becomes bothersome	In all cases	
Lower than normal numbers of red and white blood cells as well as platelets (Aplastic anaemia) Symptoms may include: fatigue, pale skin, fevers, frequent infection, tendency to bruise and bleed easily.		√	
Drug fever. Symptoms may include: fever greater than 105°F (40.5°C).		√	
Local destruction of skin cells (Lupus-like syndrome). Symptoms may include: Rash (especially when exposed to sun), fever, joint pain.		√	
A syndrome where the body produces an immune response against its own cells (Insulin autoimmune syndrome). Symptoms may include: Numbness in the extremities, low levels of blood sugar.		√	

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Inflammation of the liver (Hepatitis). Symptoms may include: Jaundice, brownish or discoloured urine and abdominal pain.		√	
Inflammation of the tissue surrounding an artery (Periarteritis). Symptoms may include: Pain in the muscles and joints.		√	
Abnormally low levels of thrombin, a component of the blood (Hypoprothrombinemia). Symptoms may include: Bleeding problems, easy bruising.		√	
Inflammation of the kidney (Nephritis).-Symptoms may include :-Reduced urine, cloudy urine, blood in urine.		√	
A decrease in white blood cells (Agranulocytosis). Symptoms may include: Sudden fever, rigors and sore throat.			√

*This is not a complete list of side effects. If you have any unexpected effects after receiving Tapazole®, contact your doctor or pharmacist.*

*Talk to your doctor or pharmacist if these symptoms are persistent or severe.*

**HOW TO STORE IT**

Store at room temperature (15-30 °C). Protect from light. Keep tightly closed.

*Keep out of reach of children.*

**REPORTING SUSPECTED SIDE EFFECTS**

**To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance.**

**You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:**

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to : **Canada Vigilance Program**  
**Health Canada**  
**Postal Locator 0701D**  
**Ottawa, ON K1A 0K9**

**Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines**

are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

*Note: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

## **MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Paladin Labs Inc., at:  
1-888-550-6060

[www.paladinlabs.com](http://www.paladinlabs.com)

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