

PRODUCT MONOGRAPH

Pr TAPAZOLE®

Methimazole Tablets, USP
5, 10 and 20 mg

Antithyroid Agent

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Pr TAPAZOLE®

Methimazole Tablets, USP

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY OF PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Oral	Tablet 5, 10 and 20 mg	Corn starch, lactose monohydrate, magnesium stearate, talc.

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.
- Patients with history of acute pancreatitis after administration of methimazole.

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.

Cardiovascular

Vasculitis

Cases of vasculitis have been observed very rarely in patients receiving methimazole therapy. The cases of vasculitis include: leukocytoclastic cutaneous vasculitis, glomerulonephritis, and systemic vasculitis (with fatal outcome). Many cases were associated with anti-neutrophilic cytoplasmic antibodies (ANCA)-positive vasculitis. Early recognition of vasculitis is important to prevent long term organ damage and/or death. Inform patients to promptly report symptoms that may be associated with vasculitis including rash, hematuria or decreased urine output, dyspnea or hemoptysis. If vasculitis is suspected, discontinue methimazole therapy and initiate appropriate intervention.

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

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 aplastic 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

Hepatotoxicity is a rare adverse reaction in patients treated with methimazole. Although there have been reports of hepatotoxicity (including acute liver failure) associated with TAPAZOLE®, the risk of hepatotoxicity appears to be less with methimazole than with propylthiouracil, especially in the pediatric population. 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**.

There have been post-marketing reports of acute pancreatitis in patients receiving methimazole. In case of acute pancreatitis, Tapazole should be discontinued immediately. Do not start treatment in patients with a history of acute pancreatitis that has been attributed to methimazole. Re-exposure may result in recurrence of acute pancreatitis with decreased time to onset. See **Post-Market Adverse Reactions** section.

Skin

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

Special Populations

Pregnant Women: Hyperthyroidism in pregnant women should be adequately treated to prevent serious maternal and fetal complications.

Methimazole can cause fetal harm when administered to a pregnant woman. Methimazole readily crosses the placental membranes and can induce goiter and hypothyroidism in the developing fetus.

Based on human experience from epidemiological studies and spontaneous reporting, methimazole is suspected to cause congenital malformations when administered during pregnancy, particularly in the first trimester of pregnancy and at high doses. Reported malformations include aplasia cutis congenital, craniofacial malformations (choanal atresia; facial dysmorphism), exomphalos, oesophageal atresia, omphalo mesenteric duct anomaly and ventricular septal defect.

Methimazole must only be administered during pregnancy after a strict individual benefit/risk assessment and only at the lowest effective dose, without additional administration of thyroid hormones. 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. Close maternal, fetal and neonatal monitoring is recommended, with adjustment of methimazole as necessary.

Women of Childbearing potential: Women of childbearing potential should use effective methods of contraception during methimazole therapy.

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/mm³), often with relative granulopenia.

Post-Market Adverse Reactions

The following adverse reactions have been reported from marketing experience with methimazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug.

Acute pancreatitis (see **Warnings and precautions** section).

Vasculitis (see **Warnings and precautions** section)

Cases of congenital anomalies have been reported in neonates, whose mothers were treated with methimazole during pregnancy: aplasia cutis congenital, craniofacial malformations (choanal atresia; facial dysmorphism), exomphalos, oesophageal atresia, omphalo-mesenteric duct anomaly, and ventricular septal defect (see **Warning and precautions** section).

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.

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 (LD₅₀) 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[®] 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[®] 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[®] 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

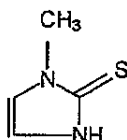
Drug Substance

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.
- If you have had problems with your pancreas after taking methimazole.

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 have had pancreatitis caused by methimazole in the past. In this case do not take Tapazole. It can make acute pancreatitis come back very quickly. Stop taking Tapazole and tell your doctor right away if you develop abdominal pain, fever, nausea or vomiting.

Female patients – talk to your doctor if:

- you are breastfeeding or planning to breastfeed
- you are pregnant or planning to become pregnant.
 - This is because Tapazole® may harm your unborn baby. Your doctor will decide if continuing to take Tapazole® is right for you and your baby.
 - Avoid becoming pregnant while you are taking Tapazole®. You should use effective methods of birth control during your treatment. If you do become pregnant while taking Tapazole®, tell your doctor right away.

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	
Rare			
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).		√	
Inflammation of the kidney (Nephritis).-Symptoms may include :-Reduced urine, cloudy urine, blood in urine.		√	
Very Rare			
Inflammation of blood vessels (vasculitis). Symptoms may include fever, headache, fatigue, weight loss, night sweats, rash, blood in urine, coughing up blood, shortness of breath.		√	
Unknown			
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.		√	
Liver problems (including Hepatitis). Symptoms may include: Jaundice, brownish or discoloured urine and abdominal pain.		√	
Inflammation of the tissue surrounding an artery (Periarthritis). 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.		√	
A decrease in white blood cells (Agranulocytosis). Symptoms may include: Sudden fever, rigors and sore throat.			√

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

Inflammation of the pancreas (acute pancreatitis): Abdominal pain. Severe stomach pain that last and gets worse when you lie down. Fever, nausea, vomiting.			√
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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 Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting(<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>); the manufacturer’s website (<http://www.paladinlabs.com>), or by calling 1-888-867-7426.

This leaflet was prepared by Paladin Labs Inc.

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