PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]APO-METHIMAZOLE

Methimazole Tablets

Tablets, 5 mg, Oral

USP

Antithyroid Agent

APOTEX INC.
150 Signet Drive
Toronto,
Ontario M9L 1T9

Date of Initial Authorization:
OCT 22, 2004

Date of Revision:
APR 05, 2022

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RECENT MAJOR LABEL CHANGES

1 INDICATIONS	04/2022
2 CONTRAINDICATIONS	08/2020
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7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women	08/2020

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

APO-METHIMAZOLE (methimazole tablets) is indicated for:

- The medical treatment of hyperthyroidism. Long-term therapy may lead to remission of the disease.
- Amelioration of hyperthyroidism in preparation for subtotal thyroidectomy or radioactive iodine therapy.
- Use when thyroidectomy is contraindicated or not advisable.

1.1 Pediatrics

Pediatrics (<18 years): No data are available to Health Canada; therefore, Health Canada has notauthorized an indication for pediatric use.

1.2 Geriatrics

Information specific to the geriatric population is not available for this drug product.

2 CONTRAINDICATIONS

APO-METHIMAZOLE (methimazole tablets) is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Nursing mothers, as the drug is excreted in breast milk.
- Patients with history of acute pancreatitis after administration of methimazole.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warning and Precautions

- Agranulocytosis (see 7 WARNINGS AND PRECAUTIONS, Hematologic and 8 ADVERSE REACTIONS)
- Liver toxicity (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic)

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Adult (≥18 years of age): 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.

Geriatric (>65 years of age): Clinical Studies of methimazole did not include sufficient numbers of subjects aged 65 or over to determine whether they respond differently from younger subjects.

In general, dose selection for an elderly patient should be cautious reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pediatric (<18 years of age): Health Canada has not authorized an indication for pediatric use.

Hepatic impairment: The dose should be kept as low as possible and patients should be closelymonitored as the plasma clearance of methimazole is reduced.

Renal impairment: The dose should be kept as low as possible and careful individual dose adjustment under close monitoring is recommended as there is a lack of data regarding the pharmacokinetic behaviour of methimazole in patients with renal impairment.

4.4 Administration

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

4.5 Missed Dose

If a dose is missed, patients should contact their healthcare professional. Patients should not take a double dose to make up for a forgotten dose. Patients should take their next scheduled dose as usual.

5 OVERDOSAGE

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.

Overdose may also lead to hypothyroidism with corresponding symptoms of a reduced

metabolism and, through the feedback effect, to activation of the adenohypophysis with subsequent goitre growth. This can be avoided by dose reduction as soon as a euthyroid metabolic condition is achieved.

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 overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

The patient's bone marrow function should be monitored.
In case of suspected overdose, patients should be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment should be instituted as required.

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/ Composition	Non-medicinal Ingredients
Oral	Tablet, 5 mg	anhydrous lactose, crospovidone and magnesium stearate

APO-METHIMAZOLE Tablets 5 mg: Each white, round, flat-faced bevelled edged tablet, engraved "APO" on one side, scored and engraved "MET" over "5" on the other, contains 5 mg methimazole. Available in bottles of 100 tablets.

In addition to the medicinal ingredient methimazole, each tablet contains the non-medicinal ingredients anhydrous lactose, crospovidone and magnesium stearate.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

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

Animal data has shown thyroid hyperplasia, thyroid adenoma and carcinoma formation (see 16 NON-CLINICAL TOXICOLOGY – carcinogenicity).**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

Hypothyroidism

APO-METHIMAZOLE (methimazole tablets) can cause hypothyroidism necessitating routine monitoring of TSH and free T4 levels with adjustments in dosing to maintain a euthyroid state. Excess dosage can lead to sub- clinical or clinical hypothyroidism and goitre growth due to TSH increase (see Respiratory).

Lactose

APO-METHIMAZOLE tablets contain anhydrous lactose. 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 9.4 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 APO-METHIMAZOLE, 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, APO-METHIMAZOLE 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 8.5 Post-Market Adverse Reactions section.

Monitoring and Laboratory Tests

The patient's liver function, hepatic transaminase levels, and the complete blood count should be closely monitored. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 7 WARNINGS AND PRECAUTIONS, Hematologic. 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. Once clinical evidence of hyperthyroidism has resolved, the finding of a rising serum TSH indicates that a lower maintenance dose of APO-METHIMAZOLE should be employed. Careful monitoring is necessary in patients with large

goitres with constriction of the trachea because of the risk of goitre growth.

Respiratory

Treating patients with intrathoracic goitres necessitates caution and monitoring since intrathoracicgoitre can grow during treatment causing tracheal obstruction. Goitre growth due to increased TSH levels may indicate excess dosage.

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

7.1 Special Populations

7.1.1 Pregnant Women

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.

7.1.2 Breast-feeding

Methimazole is excreted in human breast milk and its use is contraindicated in nursing mothers.

7.1.3 Pediatrics

Pediatrics (<18 years of age): **No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.**

7.1.4 Geriatrics

Clinical studies of methimazole did not include sufficient numbers of subjects aged 65 or over to determine whether they respond differently from younger subjects.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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 7 WARNINGS AND PRECAUTIONS.

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.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial 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^3), often with relative granulopenia.

8.5 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 7 WARNINGS AND PRECAUTIONS).

Vasculitis (see 7 WARNINGS AND PRECAUTIONS)

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 7 WARNINGS AND PRECAUTIONS).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

APO-METHIMAZOLE (methimazole tablets) may interact with anticoagulants and treatment of patients with both methimazole and warfarin necessitates intensive and frequent monitoring (see 7 WARNINGS AND PRECAUTION).

9.4 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.

As methimazole is used in the treatment of hyperthyroidism, once a patient becomes euthyroid, the following drug interactions may need to be considered:

- β-adrenergic blocking agents: Hyperthyroidism may cause an increased clearance of beta blockers with a high extraction ratio. A dose reduction of beta-adrenergic blockers may be needed when a hyperthyroid patient becomes euthyroid.
- Digitalis glycosides: Serum digitalis levels may be increased when hyperthyroid patients on a stable digitalis glycoside regimen become euthyroid; a reduced dosage of digitalis glycosides may be needed.
- Theophylline: Theophylline clearance may decrease when hyperthyroid patients on a stable theophylline regimen become euthyroid; a reduced dose of theophylline may be needed.

9.5 Drug-Food Interactions

Interactions with foods have not been studied.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been studied.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been studied.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 Pharmacodynamics

Methimazole inhibits dose-dependently the incorporation of iodine into tyrosine and thereby the neosynthesis of thyroid hormones. This property permits symptomatic therapy of hyperthyroidism regardless of its cause. Whether methimazole furthermore affects the 'natural course' taken by the immunologically induced type of hyperthyroidism (Graves' disease), i.e. whether it suppresses the underlying immunopathogenitic process, can presently not be decided with certainty. The release of previously synthesized thyroid hormones from the thyroid is not affected. This explains why the lengthof the latency period until normalization of the serum concentrations of thyroxine and triiodothyronine, and thus until clinical improvement, differs in individual cases. Hyperthyroidism due to the release of hormones after destruction of thyroid cells, e.g. after radioiodine therapy or in thyroiditis, is also not affected.

10.3 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.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C to 30°C). Preserve in well-closed, light-resistant containers.

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

None required.

PART II: SCIENTIFIC INFORMATION

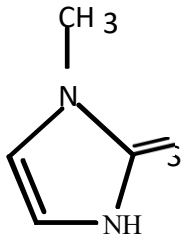
13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: Methimazole

Chemical Name(s): 1) 2*H*-Imidazole-2-thione, 1,3-dihydro-1-methyl;
2) 1-Methylimidazole-2-thiol

Structural Formula:



Molecular Formula: $C_4H_6N_2S$

Molecular Weight: 114.17 g/mol

Physicochemical properties:

Description:	A white to slightly cream coloured powder.
Solubility:	Freely soluble in water, alcohol and chloroform, slightly soluble in ether, petroleum ether and benzene.
pH:	7.8 (1% solution in water at 25ºC)
pKa:	11.9
Melting Range:	between 143ºC and 146ºC

14 CLINICAL TRIALS

14.3 Comparative Bioavailability Studies

A randomized, two-way, single dose (2 x 5 mg), cross-over comparative bioavailability study of APO-METHIMAZOLE (Apotex Inc.) and TAPAZOLE (Paladin Laboratories Inc.) was conducted in healthy, adult, male subjects under fasting conditions. Comparative bioavailability data from 27 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Methimazole (2 x 5 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	1465.89 1496.5 (21.4)	1489.58 1511.9 (18.3)	98.4	95.6 – 101.3
AUC_I (ng·h/mL)	1511.57 1543.7 (21.6)	1532.35 1555.8 (18.6)	98.6	95.9 – 101.5
C_{max} (ng/mL)	202.17 210.4 (29.9)	197.56 204.3 (27.6)	102.3	92.8 – 112.9
T_{max}[3] (h)	0.67 (0.25 – 1.50)	0.50 (0.33 – 2.00)		
$T_{½}$[4] (h)	6.81 (12.7)	6.87 (14.9)		

[1] APO-METHIMAZOLE (methimazole) tablets, 5 mg (Apotex Inc.)

[2] TAPAZOLE (methimazole) tablets, 5 mg (Paladin Laboratories Inc., Canada)

[3] Expressed as the median (range) only

[4] Expressed as the arithmetic mean (CV %) only

15 MICROBIOLOGY

No data available.

16 NON-CLINICAL TOXICOLOGY

Carcinogenicity: 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 (see 7 WARNINGS AND PRECAUTIONS).

17 SUPPORTING PRODUCT MONOGRAPHS

1. **TAPAZOLE**® (Methimazole tablets USP 5mg, 10mg and 20mg), Submission Control Number:246350, Product Monograph, Paladin Labs Inc., JUN 08, 2021.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
[Pr]APO-METHIMAZOLE

Methimazole Tablets USP

Read this carefully before you start taking **APO-METHIMAZOLE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APO-METHIMAZOLE**.

Serious Warnings and Precautions

- **Agranulocytosis (decrease in white blood cell count)**: Treatment with APO-METHIMAZOLE can cause agranulocytosis. Your healthcare professional will monitor your health for signs and symptoms ofagranulocytosis.
- **Liver toxicity (injury or damage to the liver)**: Treatment with APO-METHIMAZOLE can cause liver toxicity problems. This can lead to fulminant hepatitis (inflammation of the liver), hepatic necrosis (death of liver cells), encephalopathy (a neurological disorder), and cholestatic jaundice (yellowing of the skin or whites of eyes). If you notice any signs and symptoms of liver toxicity, tell your healthcare professional, they will also monitor your liver function.

See the **Serious side effects and what to do about them table**, below, for more information on these and other serious side effects.

What is APO-METHIMAZOLE used for?
- to treat hyperthyroidism (overactive thyroid gland).
- to treat and prepare for thyroidectomy (removal of the thyroid gland) or for radioactive iodine treatment.
- when the overactive thyroid gland cannot be removed.

How does APO-METHIMAZOLE work?
APO-METHIMAZOLE is a type of medication called antithyroid agents. It works by stopping the thyroid gland from making thyroid hormones.

What are the ingredients in APO-METHIMAZOLE?

Medicinal ingredient: Methimazole
Non-medicinal ingredients: Anhydrous lactose, crospovidone and magnesium stearate

APO-METHIMAZOLE comes in the following dosage forms:

Tablets: 5 mg.

Do not use APO-METHIMAZOLE if:
- you are allergic to methimazole or any of the ingredients in APO-METHIMAZOLE.
- you are breastfeeding. APO-METHIMAZOLE can be transferred into your breast milk.

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

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-METHIMAZOLE. Talk about any health conditions or problems you may have, including if you:

- have a low white blood cell count
- have joint pain.
- have liver problems.
- have skin problems.
- are intolerant to are intolerant to some sugars (e.g., lactose, a milk sugar which is a component of APO-METHIMAZOLE).
- have a large goitre (swelling in the front neck), the goitre may grow during treatment making it difficult to breath.
- are taking medications that are known to cause agranulocytosis (decrease in white blood cell count).

Other warnings you should know about:

APO-METHIMAZOLE can cause the following:

- **Arthralgia (joint pain):** The development of arthralgia may indicate severe transient migratory polyarthritis also known as antithyroid arthritis syndrome (pain that spreads from one joint to another). Your healthcare professional will stop your treatment if this occurs.
- **Acute pancreatitis (inflammation of the pancreas):** Methimazole therapy has been reported to cause acute pancreatitis. If you notice any signs and symptoms of acute pancreatitis, your healthcare professional will immediately stop your treatment with APO-METHIMAZOLE.
- **Exfoliative dermatitis (severe inflammation of the entire skin surface):** Tell your healthcare professional right away if you notice signs of exfoliative dermatitis such as redness or peeling of the skin over large areas of your body. Your treatment with APO-METHIMAZOLE should be stopped.
- **Vasculitis (inflammation and narrowing of blood vessels):** This can cause long-term organ damage or even be life-threatening. Tell your healthcare professional if you notice or develop any symptoms of vasculitis. They will stop your treatment and may initiate an appropriate intervention.
- **Other blood problems:** Methimazole therapy can cause:
  - leukopenia (low white blood cells),
  - thrombocytopenia (low blood platelets), and
  - aplastic anemia (when cells meant to develop into mature blood cells are damaged).

Your healthcare professional may monitor your health (including your bone marrow function) and may stop your treatment if this occurs.

See the **Serious side effects and what to do about them table**, below, for more information on these and other serious side effects.

Pregnancy:

- If you are able to get pregnant or think you are pregnant, there are specific risks you must discuss with your healthcare professional.
- Treatment with APO-METHIMAZOLE may harm your unborn baby, especially in the first trimester of pregnancy. Your healthcare professional will decide if taking APO-METHIMAZOLE is right for you and your baby.
- You should use effective methods of birth control during your treatment.
- If you become pregnant or think you are pregnant while taking APO-METHIMAZOLE, tell your healthcare professional right away.

Check-ups and testing: Your healthcare professional will monitor your health before and during your treatment. This may including having regular blood tests. This will tell your healthcare professional how APO-METHIMAZOLE is affecting you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with APO-METHIMAZOLE :

- medicines known as anticoagulants (blood thinners) such as Warfarin

How to take APO-METHIMAZOLE:

- Take APO-METHIMAZOLE exactly as prescribed by your doctor.
- APO-METHIMAZOLE is usually taken orally three times a day (every 8 hours).

Usual dose:

The initial dose is 15 mg to 60 mg per day depending on your condition. The maintenance dose is 5 mg to 15 mg per day.

Overdose:

If you take too many APO-METHIMAZOLE tablets, you may experience:

- Nausea
- vomiting
- stomach discomfort
- headaches
- fever
- joint pain
- rashes
- edema (fluid retention or swelling)

If you think you, or a person you are caring for, have taken too much APO-METHIMAZOLE, contact a health care professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed dose:

Talk to your healthcare professional if you miss one of your scheduled doses of APO-METHIMAZOLE. You should not take a double dose to make up for a forgotten dose. Take your next scheduled dose as usual.

What are possible side effects from using APO-METHIMAZOLE?

These are not all the possible side effects you may have when taking APO-METHIMAZOLE. If you experience any side effects not listed here, tell your healthcare professional.

Some common side effects include:

- anorexia (an eating disorder)
- dizziness
- drowsiness
- edema (swelling due to fluid build up)
- hair loss
- heart burn
- muscle pain
- neuritis (inflammation of a nerve, often with pain or tenderness)
- numbness
- sialadenopathy and lymphadenopathy (lymph node diseases)
- hives (urticaria)
- skin pigmentation
- loss of taste
- vertigo

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Agranulocytosis (decrease in white blood cell count): frequent infection with fever, chills, sore throat.			✓
Liver problems (including hepatitis): abdominal pain, yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea, vomiting, unusual dark urine, unusual tiredness.		✓	
RARE			
Aplastic anemia			

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
(when cells meant to develop into mature blood cells are damaged): fatigue, weakness, pale skin, fevers, frequent infection, tendency to bruise and bleed easily.		✓	
Drug fever: fever greater 40.5 ˚C (105˚F).		✓	
Nephritis (inflammation of the kidney): decreased appetite, difficulty breathing, fatigue, frequent urination, itchiness, nausea, vomiting.		✓	
VERY RARE			
Vasculitis (inflammation of blood vessels): fever, headache, fatigue, weight loss, night sweats, rash, blood in urine, coughing up blood, shortness of breath.		✓	
UNKNOWN			
Insulin autoimmune syndrome (an immune response against your body's own cells that causes low blood sugar): numbness in the extremities, low		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
levels of blood sugar.			
Lupus-like syndrome (when your body's immune system attacks your own tissues and organs, including your joints, skin, kidneys, blood cells, heart and lungs): fatigue, fever, joint pain, stiffness and swelling, rash on the face that covers the cheeks and the bridge of the nose or rashes elsewhere on the body, skin lesions, shortness of breath, chest pain, dry eyes, headaches, confusion, memory loss.		✓	
Acute pancreatitis (Inflammation of the pancreas): upper abdominal pain, severe stomach pain that last and gets worse when you lie down, rapid heartbeat, fever, nausea, vomiting.			✓
Hypoprothrombinemia (abnormally low levels of prothrombin, used for blood-clotting):		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
bleeding problems, easy bruising.			
Periarteritis (Inflammation of the tissue surrounding an artery): pain in the muscles and joints.		✓	
Arthralgia (joint pain).		✓	
Exfoliative dermatitis (severe inflammation of the entire skin surface): redness or peeling of the skin over large areas of your body.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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.

Storage:

Store at room temperature (15°C to 30°C). Preserve in well-closed, light-resistant containers.

Keep out of the reach and sight of children.

If you want more information about APO-METHIMAZOLE:

- 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://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html). Find the Patient Medication Information on the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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