PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] MAR-METHIMAZOLE

Methimazole

Tablets 5 mg and 10 mg, oral

USP

Antithyroid Agent

Marcan Pharmaceuticals Inc.
2 Gurdwara Road, Suite 112
Ottawa, Ontario
Canada K2E 1A2

Date of Initial Authorization:
August 14, 2018

Date of Revision:
October 10, 2023

Submission Control Number: 276209

RECENT MAJOR LABEL CHANGES

7 Warnings and Precautions	01/2022

TABLE OF CONTENTS

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

MAR-METHIMAZOLE is indicated in adults 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 not authorized an indication for pediatric use.

1.2. Geriatrics

Geriatrics (≥ 65 years): Clinical studies did not include sufficient numbers of subjects aged 65 years or older to determine the safety and efficacy of methimazole in this geriatric population (see 4.2 Recommended Dose and Dosage Adjustment and 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

MAR-METHIMAZOLE 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.
- Breastfeeding women, 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 Warnings 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

4.1 Dosing Considerations

- MAR-METHIMAZOLE treatment can cause hypothyroidism and adjustments in dosing are necessary to maintain a euthyroid state (see Endocrine and Metabolism, *Hypothyroidism*). Excess dosage should be avoided as it can lead to sub-clinical or clinical hypothyroidism and goitre growth (see Respiratory). Periodic monitoring of thyroid function should be performed with dosage adjustments

as necessary and with more careful monitoring in patients with large goitres (see Monitoring and Laboratory Tests).

- Concomitant administration of MAR-METHIMAZOLE and warfarin necessitates intensive and frequent monitoring, particularly when initiating, discontinuing, or changing doses of methimazole (see Hematologic, *Anticoagulant Therapy* and 9.4 Drug-Drug Interactions).
- MAR-METHIMAZOLE can 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. Women of childbearing potential should use effective methods of contraception during MAR-METHIMAZOLE therapy (see 7.1.1 Pregnant Women).

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 (see 7.1.3 Pediatrics).

Hepatic impairment: The dose should be kept as low as possible and patients should be closely monitored as the plasma clearance of methimazole is reduced (see Monitoring and Laboratory Tests).

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

- MAR-METHIMAZOLE is administered orally.
- MAR-METHIMAZOLE is usually given in three equal doses per day at approximately eight-hour intervals.
- Patients should wash their hands with soap and water after handling the tablet, particularly if they have to break the tablet.
- Methimazole should not be handled by pregnant women and children.

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 and 10 mg of methimazole	lactose monohydrate, magnesium stearate, starch and talc

5 mg tablets: Round white to off white bi-convex tablet. Debossed **HP bisect 70** on one side and plain on reverse side.

10 mg tablets: Round white to off white bi-convex tablet. Debossed **HP bisect** 71 on one side and plain on reverse side.

MAR-METHIMAZOLE tablets are supplied in bottles of 100.

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.

Driving and Operating Machinery

Patients should be warned to exercise caution when driving or operating machinery while on treatment with MAR-METHIMAZOLE. Adverse reactions of vertigo and drowsiness were reported with MAR-METHIMAZOLE treatment (see 8.1 Adverse Reaction Overview).

Endocrine and Metabolism

Hypothyroidism

Methimazole 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

MAR-METHIMAZOLE contains 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 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 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, 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 and Hepatic/Biliary/Pancreatic. 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 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.

Reproductive Health: Female and Male Potential

see 7.1.1 Pregnant Women.

- **Fertility**

No data exist regarding the effect of MAR-METHIMAZOLE on fertility.

- **Teratogenic Risk**

Methimazole can cause fetal harm when administered to a pregnant woman. Methimazole has been reported to cause congenital malformations when administered during pregnancy, particularly in the first trimester of pregnancy and at high doses. If MAR-METHIMAZOLE is used during pregnancy or if the patient becomes pregnant while taking MAR-METHIMAZOLE, the patient should be warned of the potential hazard to the fetus. Women of childbearing potential should use effective methods of contraception during methimazole therapy (see 7.1.1 Pregnant Women).

Respiratory

Treating patients with intrathoracic goitres necessitates caution and monitoring since intrathoracic goitre 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, omphalomesenteric 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 methimazole, 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 breastfeeding women (see 2 CONTRAINDICATIONS).

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

Geriatrics (≥ 65 years) 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.

Acute pancreatitis (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Vasculitis (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

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, omphalomesenteric duct anomaly, and ventricular septal defect (see 7.1.1 Pregnant Women).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Methimazole may interact with anticoagulants and treatment of patients with both methimazole and warfarin necessitates intensive and frequent monitoring (see 7 WARNINGS AND PRECAUTION, Hematologic, Anticoagulant Therapy).

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 length of 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: Methimazole is metabolized rapidly in the liver and requires frequent administration.

Elimination: Methimazole is excreted in the urine.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15 °C to 30 °C). Protect from light. Keep tightly closed. Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

None required.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

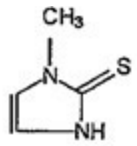
Proper name: Methimazole / Thiamazole

Chemical name: 2H-Imidazole-2-thione

Molecular formula and molecular mass: $C_4H_6N_2S$

114.2 g / mol

Structural formula:



Physicochemical properties:

Description:	White to pale buff crystalline powder with a characteristic odour. 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

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized are not available.

14.3 Comparative Bioavailability Studies

A randomized, double-blind, balanced, two-treatment, two-period, two-sequence, single dose, two-way crossover, bioequivalence study of Mar-Methimazole (Methimazole) 10 mg tablets (Marcan Pharmaceuticals Inc.) with PrTAPAZOLE® (Methimazole) 10 mg tablets (Paladin Labs Inc.) in 34 healthy, adult, human male subjects, under fasting conditions.

Methimazole (1 x 10 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	1925.58 1952.39 (16.85)	1915.94 1944.09 (17.65)	100.50	97.97 – 103.11
AUC_I (ng.h/mL)	2163.70 2201.02 (18.90)	2157.42 2200.10 (20.67)	100.29	97.29 – 103.38
C_{max} (ng/mL)	274.57 282.06 (23.44)	292.92 300.08 (22.52)	93.74	86.26 – 101.86
T_{max}§ (h)	0.50 (0.17-1.50)	0.50 (0.33-1.50)		
$T_{½}$€ (h)	7.62 (15.65)	7.75 (21.43)		

* Mar-Methimazole 10 mg tablets; Manufactured by Marcan Pharmaceuticals Inc., Ottawa, Canada
† PrTapazole (Methimazole 10 mg tablets); Manufactured by Paladin Labs Inc., Canada, was purchased in Canada.
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

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, Carcinogenesis and Mutagenesis).

17 SUPPORTING PRODUCT MONOGRAPHS

1. TAPAZOLE®, Tablets, 5 mg and 10 mg submission control number 270311, Product Monograph, Paladin Labs Inc. April 13, 2023.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrMAR-METHIMAZOLE

Methimazole Tablets

Read this carefully before you start taking **Mar-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 **Mar-Methimazole**.

Serious Warnings and Precautions

- **Agranulocytosis (decrease in white blood cell count)**: Treatment with Mar-Methimazole can cause agranulocytosis. Your healthcare professional will monitor your health for signs and symptoms of agranulocytosis.
- **Liver toxicity (injury or damage to the liver)**: Treatment with Mar-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 MAR-METHIMAZOLE used for?
Mar-Methimazole is used in adults:
- 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 MAR-METHIMAZOLE work?
Mar-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 MAR-METHIMAZOLE?
Medicinal ingredient: Methimazole
Non-medicinal ingredients: Lactose monohydrate, magnesium stearate, starch and talc.

MAR-METHIMAZOLE comes in the following dosage forms:
Tablets: 5 mg and 10 mg

Do not use MAR-METHIMAZOLE if:
- you are allergic to methimazole or any of the ingredients in Mar-Methimazole.
- you are breastfeeding. Mar-Methimazole can be transferred into your breast milk.
- you have or 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 Mar-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 some sugars (e.g., lactose, a milk sugar which is a component of Mar-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:

Mar-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):** Mar-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 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 Mar-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:** Mar-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 Mar-Methimazole may harm your unborn baby, especially in the first trimester of pregnancy. Your healthcare professional will decide if taking Mar-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 Mar-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 include having regular blood tests. This will tell your healthcare professional how Mar-Methimazole is affecting you.

Driving and using machines: MAR-METHIMAZOLE can cause tiredness and a sense of spinning dizziness. Before you drive or do tasks that require special attention, wait until you know how you respond to MAR-METHIMAZOLE.

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 Mar-Methimazole:

- medicines known as anticoagulants (blood thinners) such as warfarin.

How to take MAR-METHIMAZOLE:

- Take Mar-Methimazole exactly as prescribed by your doctor.
- Mar-Methimazole is usually taken orally three times a day (every 8 hours).
- Patients should wash their hands with soap and water after handling the tablet, particularly if they have to break the tablet.
- Mar-Methimazole should not be handled by pregnant women and children.

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 Mar-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 Mar-Methimazole, contact a healthcare 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 Mar-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 Mar-Methimazole?

These are not all the possible side effects you may have when taking Mar-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
- hives (urticaria)
- loss of taste
- muscle pain
- neuritis (inflammation of a nerve, often with pain or tenderness)
- numbness
- sialadenopathy and lymphadenopathy (lymph node diseases)
- skin pigmentation
- 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 (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 than 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			
Acute pancreatitis (inflammation of the pancreas): upper abdominal pain, severe stomach pain that last and gets worse when you lie down, rapid heart beat, fever, nausea, vomiting.			✓
Arthralgia (joint pain).		✓	
Exfoliative dermatitis (severe inflammation of the entire skin surface)**:** redness or peeling of the skin over large areas of your body.		✓	
Hypoprothrombinemia (abnormally low levels of prothrombin, used for blood-clotting): bleeding problems, easy bruising.		✓	
Hypothyroidism (underactive/low thyroid): Weight gain, tiredness, hair loss, muscle weakness, feeling cold, dry skin, constipation, puffy face, heavier than		✓	

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	
normal or irregular menstrual periods, enlarged thyroid gland.			
Insulin autoimmune syndrome (an immune response against your body's own cells that causes low blood sugar): numbness in the extremities, low 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.		✓	
Periarteritis (inflammation of the tissue surrounding an artery): pain in the muscles and joints.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough 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). Protect from light. Keep the bottle tightly closed.
Keep out of reach and sight of children.

If you want more information about MAR-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); Marcan Pharmaceuticals Inc.'s website www.marcanpharma.com, or by calling 1-855-627-2261.

This leaflet was prepared by Marcan Pharmaceuticals Inc.
Last Revised: October 10, 2023