PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrMETHOPRAZINE

Methotrimeprazine Maleate Tablets

Tablets, 2 mg, 5 mg, 25 mg and 50 mg, Oral

Neuroleptic

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

METHOPRAZINE (Methotrimeprazine Maleate Tablets) is indicated for:

- **Psychotic disturbances**: acute and chronic schizophrenias, senile psychoses, manic-depressive syndromes.
- **Analgesic**: In pain due to cancer, zona, trigeminal neuralgia, neurocostal neuralgia, in phantom limb pains, muscular discomforts and as post-operative analgesic adjunct.
- **Anti-emetic**: For the treatment of nausea and vomiting of central origin.
- **Sedative**: For the management of insomnia.

1.1 Pediatrics

Pediatrics (<1 year of age): METHOPRAZINE is contraindicated in children younger than 1 year. See 2 CONTRAINDICATIONS.

Pediatrics (1 to 18 years of age): See 4.2 Recommended Dose and Dosage Adjustment; and 7.1.3 Pediatrics.

1.2 Geriatrics

Geriatrics (≥65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. See 4.2 Recommended Dose and Dosage Adjustment; and 7.1.4 Geriatrics.

METHOPRAZINE is not indicated for the treatment of patients with dementia. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

2 CONTRAINDICATIONS

METHOPRAZINE is contraindicated in Children younger than 1 year, due to a possible association between use of phenothiazine-containing products and Sudden Infant Death Syndrome (SIDS).

METHOPRAZINE (methotrimeprazine maleate tablets) is contraindicated in patients with:

- Hypersensitivity to methotrimeprazine, other phenothiazines, 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.
- Coma or CNS depression due to alcohol, hypnotics, analgesics or narcotics.
- Concomitant neuroleptics including dopaminergics.
- Blood dyscrasia, including agranulocytosis.

- Bone marrow depression.
- Hepatic impairment.
- Brain damage.
- Pheochromocytoma.
- Circulatory collapse/severe hypotension, or severe heart disorder.
- Myasthenia gravis.
- Regional or spinal anesthesia.
- Risk of urinary retention related to urethroprostatic disorders.
- Risk of closed angle glaucoma.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Increased mortality in elderly patients with dementia:** Elderly patients with dementia treated with antipsychotic drugs are at an increased risk of death compared to those treated with placebo. METHOPRAZINE is not approved for use in elderly patients with dementia. See 7.1.4 Geriatrics.
- Neuroleptic malignant syndrome (NMS) is a rare, sometimes fatal, neurological disorder that has been reported in association with antipsychotics drugs including METHOPRAZINE. See 7 WARNINGS AND PRECAUTIONS, Neurologic and 8.5 Post-Market Adverse Reactions.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Dosage must be adjusted according to the indication and individual needs of the patient. If sedation during the day is too pronounced, lower doses may be given during the day and higher doses at night.
- In high oral doses, orthostatic hypotension may be encountered at the start of treatment. Patients whose treatment is started with high oral doses should be kept in bed during the first few days.
- Medical and laboratory evaluations should be performed prior to initiation of treatment, to rule out cardiovascular risk factors (in particular ventricular arrhythmia and QT prolongation). See 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 8.5 Post-Market Adverse Reactions.
- METHOPRAZINE therapy should be initiated at low doses in patients with arteriosclerosis or cardiovascular problems.

- Careful monitoring of treatment with METHOPRAZINE is required in patients with certain cardiovascular diseases, due to the quinidine-like, tachycardia inducing and hypotensive effects of this product class. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 5 OVERDOSAGE.
- All potential risk factors for venous thromboembolism (VTE) should be identified and preventive measures undertaken prior to initiation of treatment with METHOPRAZINE. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 8.2 Clinical Trial Adverse Reactions, Vascular disorders.
- Because of its anticholinergic effects, METHOPRAZINE must be administered with caution in patients with glaucoma and prostatic hypertrophy.
- During long-term therapy, periodic liver function tests should be performed. In addition, complete blood counts (CBC), white blood cell count (WBC) should be conducted regularly, particularly during the first 2 or 3 months of treatment, and physicians should watch for any signs of blood dyscrasia.
- METHOPRAZINE should be used with caution in epileptic patients, since phenothiazines, including METHOPRAZINE, may lower the seizure threshold. See 7 WARNINGS AND PRECAUTIONS, Neurologic and 8.2 Clinical Trial Adverse Reaction. It is advisable to administer an appropriate anticonvulsant medication to epileptic patients receiving METHOPRAZINE therapy.
- Careful monitoring of patients with severe renal impairment is recommended, due to the risk of accumulation.
- Patients should have baseline and periodic monitoring of blood glucose and body weight.
- Because of the risk of photosensitization, patients should be advised to avoid exposure to direct sunlight.
- Patients are strongly advised not to consume alcoholic beverages or to take medicines containing alcohol during treatment with METHOPRAZINE.
- Phenothiazines may be additive with, or may potentiate the action of, other CNS depressants such as opiates or other analgesics, barbiturates or other sedatives, general anesthetics, or alcohol.

4.2 Recommended Dose and Dosage Adjustment

Adults

Minor conditions in which METHOPRAZINE may be given in low doses as a tranquilizer, anxiolytic, analgesic or sedative: begin treatment with 6 mg/day to 25 mg/day in 3 divided doses at mealtimes. Increase the dosage until the optimum level has been reached. As a sedative, a single night time dose of 10 mg to 25 mg is usually sufficient.

Severe Conditions such as pyschosis or intense pain in which METHOPRAZINE is employed at higher doses: Begin treatment with 50 mg/day to 75 mg/day divided into 2 or 3 daily doses; increase the dosage until the desired effect is obtained. In certain psychotics, doses may reach 1 g or more/day. If it is necessary to start therapy with higher doses, i.e., 100 mg/day to 200 mg/day, administer the drug in divided daily doses and keep the patient in bed for the first few days.

Pediatrics (1 to less than 18 years of age)

The initial dose has been established at 0.25 mg/kg daily in 2 or 3 divided doses. This dosage may be increased gradually until an effective level is reached which should not surpass 40 mg/day for a child less than 12 years of age. See 7.1.3 Pediatrics.

Geriatrics (≥65 years of age)

METHOPRAZINE should be used cautiously in the elderly owing to their susceptibility to drugs acting on the central nervous system and a lower initial dosage is recommended. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 7.1.4 Geriatrics.

Hepatic Impairment:

METHOPRAZINE is contraindicated in patients with hepatic impairment (see 2 CONTRAINDICATIONS).

Renal Impairment:

METHOPRAZINE should not be used in patients with renal insufficiency. See 7 WARNINIGS AND PRECAUTIONS, Renal.

4.2.1 Discontinuing Treatment

Acute withdrawal symptoms, including nausea, vomiting, headache, anxiety, agitation, dyskinesia, dystonia, disturbed temperature regulation, and insomnia, have very rarely been reported following the abrupt cessation of high doses of neuroleptics.

Relapse may also occur, and the emergence of extrapyramidal reactions has been reported. Therefore, gradual withdrawal is advisable. Symptoms of withdrawal can occur following treatment at any dose.

Withdrawal of treatment should occur under close medical supervision.

4.4 Administration

Tablets are for oral administration.

4.5 Missed Dose

If a dose is missed, it should be taken promptly, unless it is near the time of the next dose, in which case the missed dose should be skipped. The next dose should be taken at the regular time. Doses should not be doubled.

5 OVERDOSAGE

High doses cause depression of the central nervous system, presenting as lethargy, dysarthria, ataxia, stupor, reduction in consciousness into coma, convulsions; mydriasis; cardiovascular symptoms (related to risk of QT interval prolongation), such as hypotension, ventricular tachycardia and arrhythmia; respiratory depression; hypothermia. These effects may be potentiated by other medicines or by alcohol. Anticholinergic syndrome may occur. Severe parkinsonian syndrome may occur.

Symptoms

Symptoms of acute intoxication may include simple CNS depression, spasms, tremor or tonic and clonic convulsions, coma accompanied by hypotension and respiratory depression.

Treatment

There is no specific antidote. Treatment is symptomatic. Centrally acting emetics are ineffective because of the anti-emetic action of METHOPRAZINE.

Hypotension: A 5% glucose solution may be administered. If a hypertensive agent is required, norepinephrine or phenylephrine may be used, but not epinephrine which can aggravate hypotension.

Respiratory depression: Oxygen by inhalation or controlled respiration after tracheal intubation.

Respiratory infection: Wide spectrum antibiotics.

Extrapyramidal reactions: An antiparkinsonian agent or chloral hydrate, however the latter must be used with caution because of its depressant effect on respiration.

Any CNS stimulant should be used with caution.

For management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

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 2 mg, 5 mg, 25 mg and 50 mg of methotrimeprazine	Carnauba wax, colloidal silicon dioxide, corn starch, d & c yellow #10 aluminum lake 14-18%, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sunset yellow aluminum lake 40% and titanium dioxide.

Description

METHOPRAZINE 2 mg: Each yellow, round, biconvex, film-coated tablet with straight edges, engraved '2' on one side, plain on the other side, contains methotrimeprazine maleate equivalent to 2 mg of methotrimeprazine. Available in bottles of 100 and 500 tablets.

METHOPRAZINE 5 mg: Each yellow, round, biconvex, film-coated tablet with straight edges, engraved '5' on one side, plain on the other side, contains methotrimeprazine maleate equivalent to 5 mg of methotrimeprazine. Available in bottles of 100 and 500 tablets.

METHOPRAZINE 25 mg: Each yellow, round, biconvex, film-coated tablet with straight edges, engraved 'MT' over '25' on one side, plain on the other side, contains methotrimeprazine maleate equivalent to 25 mg of methotrimeprazine. Available in bottles of 100 and 500 tablets.

METHOPRAZINE 50 mg: Each yellow, round, biconvex, film-coated tablet with straight edges, engraved 'MT' over '50' on one side, plain on the other side, contains methotrimeprazine maleate equivalent to 50 mg of methotrimeprazine. Available in bottles of 100 and 500 tablets.

7 WARNINGS AND PRECAUTIONS

See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Body Temperature Regulation: Phenothiazines like METHOPRAZINE may impair sensitivity and adaptation to changes of environmental temperature so that fatal hyperthermia and heat strokes are possible complications. Appropriate care is advised when prescribing METHOPRAZINE for patients who will be experiencing conditions which may contribute to an elevation of core temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Cardiovascular

METHOPRAZINE is contraindicated in patients with circulatory collapse/severe hypotension, or severe heart disorder. See 2 CONTRAINDICATIONS. It should also be avoided in patients with cardiac failure.

Hypotension: Hypotension, which is typically orthostatic, may occur, especially in elderly, in alcoholic patients and/or at the start of treatment with high oral doses. Patients whose treatment is starting with high oral doses should be kept in bed during the first few days.

QT interval prolongation: As with other neuroleptics, very rare cases of QT interval prolongation have been reported with methotrimeprazine maleate tablets. Neuroleptic phenothiazines may potentiate QT interval prolongation, which increases the risk of onset of serious ventricular arrhythmias of the torsade de pointes type, which is potentially fatal (sudden death). QT prolongation is exacerbated, in particular, in the presence of bradycardia, hypokalemia, and congenital or acquired (i.e., drug induced) QT prolongation. If the clinical situation permits, medical and laboratory evaluations should be performed to rule out possible risk factors before initiating treatment with a neuroleptic agent and as deemed necessary during treatment. See 8.2 Clinical Trial Adverse Reactions, Cardiac disorders and 9.4 Drug-Drug

Interactions.

Vascular disorders: Venous thromboembolism (VTE), including fatal pulmonary embolism, has been reported with antipsychotic drugs, including methotrimeprazine maleate tablets, in case reports and/or observational studies. See 8.2 Clinical Trial Adverse Reactions. When prescribing METHOPRAZINE all potential risk factors for VTE should be identified and preventative measures undertaken.

In randomized, placebo-controlled, clinical trials placebo performed in a population of elderly patients with dementia and treated with certain atypical antipsychotic drugs, a 3-fold increased risk of cerebrovascular events has been observed. The mechanism of this risk increase is not known. An increase in the risk with other antipsychotic drugs or other populations of patients cannot be excluded.

METHOPRAZINE should be used with caution in patients with stroke risk factors or with a history of stroke as well as patients with risk factors for thromboembolism. See 7.1.4 Geriatrics.

Dependence, Tolerance and/or Abuse Liability

In general, phenothiazines do not produce psychic dependence. However, gastritis, nausea, vomiting, dizziness, and tremulousness have been reported following abrupt cessation of high dose therapy. See 4.2.1 Discontinuing Treatment.

Driving and Operating Machinery

METHOPRAZINE, like other antipsychotics, has the potential to impair judgement, thinking, or motor skills.

Patients should be warned about drowsiness, dizziness, and blurred vision and advised not to drive or operate machinery or engage in activities that require alertness or physical coordination, particularly during the early days of treatment, until they know how METHOPRAZINE affects them.

Endocrine and Metabolism

METHOPRAZINE should be avoided in patients with hypothyroidism. It is contraindicated in patients with pheochromocytoma. See 2 CONTRAINDICATIONS.

Hyperglycemia: Hyperglycemia or intolerance to glucose has been reported in patients treated with methotrimeprazine maleate tablets. Diabetic ketoacidosis (DKA) has occurred in patients with no reported history of hyperglycemia. Patients should have baseline and periodic monitoring of blood glucose and body weight.

Hyperprolactinemia: Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone mineral density in both female and male subjects.

Gastrointestinal

The onset of paralytic ileus, which may be manifested by distension and abdominal pain, should be treated as an emergency.

Very rare cases of potentially life-threatening necrotizing colitis have been reported. See 8.2 Clinical Trial Adverse Reactions, Gastrointestinal disorders.

Genitourinary

Rare cases of priapism have been reported with antipsychotic use, such as methotrimeprazine maleate tablets. This adverse reaction, as with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment. The most likely mechanism of action of priapism is a relative decrease in sympathetic tone.

Hematologic

METHOPRAZINE is contraindicated in patients with blood dyscrasia, including bone marrow depression and agranulocytosis. See 2 CONTRAINDICATIONS.

Neutropenia, leukopenia, granulocytopenia and agranulocytosis have been reported during antipsychotic use. Therefore, it is recommended that patients have their complete blood count (CBC) and white blood cell count (WBC) tested prior to starting METHOPRAZINE and then periodically throughout treatment. Most cases of agranulocytosis associated with the administration of phenothiazine derivatives have occurred between the fourth and tenth week of treatment. Therefore, observe patients on prolonged therapy with particular care during that time for the appearance of such signs as sore throat, fever and weakness. The occurrence of unexplained infections or fever may be evidence of blood dyscrasia and requires immediate hematological investigation. See 8 ADVERSE REACTIONS.

Hepatic/Biliary/Pancreatic

METHOPRAZINE is contraindicated in patients with hepatic impairment. See 2 CONTRAINDICATIONS.

Immune

METHOPRAZINE is contraindicated in patients with myasthenia gravis. See 2 CONTRAINDICATIONS.

Monitoring and Laboratory Tests

The following assessments should be done before and periodically during treatment with METHOPRAZINE.

- Blood glucose and body weight
- Complete blood count (CBC)
- WBC and differential counts and liver function tests
- Sore throat, fever and weakness in patients on prolonged therapy may indicate agranulocytosis. If these symptoms appear, discontinue the drug and perform liver function tests
- Blood pressure
- Renal function

Neurologic

METHOPRAZINE is contraindicated in patients with brain damage. See 2 CONTRAINDICATIONS.

METHOPRAZINE is not indicated for the treatment of patients with dementia. See 3 WARNINGS AND PRECAUTIONS BOX; 7.1.4 Geriatrics.

Seizures: METHOPRAZINE should be used with caution in epileptic patients, since phenothiazines, including METHOPRAZINE, may lower the seizure threshold. It is advisable to administer an appropriate anticonvulsant medication to epileptic patients receiving METHOPRAZINE therapy.

Neuroleptic Malignant Syndrome: A potentially fatal symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported in association with antipsychotic drugs, including methotrimeprazine maleate tablets. See 3 SERIOUS WARNINGS AND PRECAUSIONS BOX.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If NMS is suspected, immediately discontinue METHOPRAZINE and provide intensive symptomatic treatment and monitoring.

In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs, including METHOPRAZINE, and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. See 8.5 Post-Market Adverse Reactions.

Parkinson's disease: Apart from exceptional situations, METHOPRAZINE should not be used in patients with Parkinson's disease.

Tardive Dyskinesia: A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with conventional antipsychotic drugs. Although the prevalence of tardive dyskinesia with conventional antipsychotics appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the beginning of treatment, which patients are likely to develop the syndrome. See 8.2 Clinical Trials Adverse Reactions, Nervous system disorders.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic drug treatment is withdrawn.

Antipsychotic drug treatment itself, however, may suppress (or partially suppress) the signs and symptoms of tardive dyskinesia and thereby may possibly mask the underlying process.

The effect that symptom suppression has upon the long-term course of the syndrome is unknown.

METHOPRAZINE should be prescribed in a manner that is most likely to minimize the risk of tardive dyskinesia. The lowest effective dose and the shortest duration of treatment should be used, and treatment should be discontinued at the earliest opportunity, or if a satisfactory response cannot be obtained. If the signs and symptoms of tardive dyskinesia appear during treatment, discontinuation of METHOPRAZINE should be considered.

Ophthalmologic

METHOPRAZINE is contraindicated in patients with risks of closed angle glaucoma. See 2 CONTRAINDICAITONS.

Phenothiazines have been associated with retinopathy and lenticular or corneal deposits. Discontinue METHOPRAZINE if retinal changes are observed.

Peri-Operative Considerations

METHOPRAZINE is contraindicated in patients who will receive spinal or general anesthesia. See 2 CONTRAINDICATIONS.

Psychotic patients on large doses of a phenothiazine drug who are undergoing surgery should be watched carefully for possible hypotensive phenomena. Moreover, it should be remembered that reduced amounts of anesthetics or CNS depressants may be required.

Renal

METHOPRAZINE is contraindicated in patients with risks of urinary retention related to urethroprostatic disorders. See 2 CONTRAINDICATIONS. It should be avoided in patients with renal dysfunction or prostate hypertrophy.

Monitor the renal function of patients on long-term therapy with METHOPRAZINE, due to the risk of accumulation. If abnormal values are observed, discontinue the drug. Patients who may develop urinary retention should be carefully observed. This drug should not be used in patients with renal insufficiency.

Reproductive Health

- **Fertility**

  There are no fertility data in animals. In humans, because of the interaction with dopamine receptors, METHOPRAZINE may cause hyperprolactinemia which can be associated with impaired fertility in women. Some data suggest that METHOPRAZINE treatment is associated with impaired fertility in men.

Sensitivity/Resistance

Hypersensitivity reactions including urticaria and angioedema have been reported with methotrimeprazine maleate tablets use. In case of allergic reaction, treatment with METHOPRAZINE must be discontinued and appropriate symptomatic treatment initiated. See 8.5 Post-Market Adverse Reactions, Immune system disorders.

Skin

Photosensitivity may occur. Patients should use sunscreens when exposed to sunlight for prolonged periods of time.

7.1 Special Populations

7.1.1 Pregnant Women

The use of METHOPRAZINE is not recommended during pregnancy and in women of childbearing potential not using contraception unless the potential benefits outweigh the potential risks to the fetus.

Non-Teratogenic Effects: Neonates exposed to antipsychotic drugs (including METHOPRAZINE) during the third trimester of pregnancy are at risk for:

- neurological disorders such as extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence.
- various degrees of respiratory disorders ranging from tachypnoea to respiratory distress and bradycardia. Although these events occurred most often when other drugs such as psychotropic or antimuscarinic drugs were coadministered, they may also occur with antipsychotic use alone.
- signs related to atropinic properties of phenothiazines such as meconium ileus, delayed meconium passage, abdominal bloating, tachycardia and initial feeding difficulties in neonates can also occur.

These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Appropriate monitoring and treatment of neonates born to mothers receiving METHOPRAZINE are recommended.

Congenital malformations: Animal studies are insufficient with respect to reproductive toxicity. Most studies indicate that these agents are not teratogenic but there are reports of defects in infants exposed to these drugs *in utero* during the first trimester. Risk of congenital malformations cannot be excluded.

7.1.2 Breastfeeding

Phenothiazines, including methotrimeprazine maleate, are excreted in milk, therefore, breastfeeding is not recommended during treatment with METHOPRAZINE.

7.1.3 Pediatrics

Pediatrics (<1 year of age): METHOPRAZINE is contraindicated in children younger than 1 year. See 2 CONTRAINDICATIONS.

Pediatrics (1 to 18 years of age): The dosage should be titrated gradually until reaching an effective level. It should not exceed 40 mg/day for children under 12 years of age. See 4.2 Recommended Dose and Dosage Adjustment.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness.

Careful monitoring of treatment with METHOPRAZINE is required when administered in elderly patients exhibiting greater susceptibility to orthostatic hypotension, sedation, and extrapyramidal effects; chronic constipation (risk of ileus paralytic); possible prostatic hypertrophy.

Paralytic ileus, even resulting in death, may occur, appropriate measures should be taken if constipation develops.

METHOPRAZINE should be used cautiously in the elderly owing to their susceptibility to drugs acting on the central nervous system and a lower initial dosage is recommended. There is an increased risk of drug induced Parkinsonism in the elderly particularly after prolonged use.

METHOPRAZINE should be used with caution in the elderly, particularly during very hot or very cold weather (risk of hyper-, hypothermia).

Use in Geriatric Patients with Dementia

METHOPRAZINE is not indicated for the treatment of elderly patients with dementia-related psychosis. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Overall Mortality: In a meta-analysis of 13 controlled clinical trials, elderly patients with dementia treated with atypical antipsychotic drugs had an increased risk of mortality compared to placebo.

Observational studies suggest that, similar to atypical antipsychotics, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

Cerebrovascular Adverse Events (CVAEs) including stroke in Elderly Patients with Dementia: A 3-fold increase in risk of cerebrovascular adverse events has been seen in the dementia population in randomized clinical trials versus placebo with some atypical antipsychotics. The mechanism for this increased risk is not known. There is insufficient data to know if there is an increased risk of cerebrovascular events associated with METHOPRAZINE. An increased risk with other antipsychotic drugs or with other populations of patients cannot be excluded.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse effects with different phenothiazines vary in type, frequency, and mechanism of occurrence, i.e., some are dose-related, while others involve individual patient sensitivity. Some adverse effects may be more likely to occur, or occur with greater intensity, in patients with special medical problems, e.g., patients with mitral insufficiency or pheochromocytoma have experienced severe hypotension following recommended doses of certain phenothiazines.

Phenothiazines have been observed to exert marked sedative effects and have a definite potential to induce parkinsonian syndrome, cause cholestatic hepatitis with intrahepatic obstructive jaundice and precipitate dermatological reactions.

8.2 Clinical Trial Adverse Reactions

Not all of the following adverse reactions have been reported with every phenothiazine derivative, but they have been reported with one or more, and should be borne in mind when drugs of this class are administered.

Blood and lymphatic system disorders: Rare instances of agranulocytosis have been reported. Cases of neutropenia and granulocytopenia have also been reported.

Cardiac disorders: Rare cardiac rhythm disturbances, including tachycardia or fibrillation have occurred.

Very rare cases of QT interval prolongation have been reported. There have been isolated reports of sudden death, with possible causes of cardiac origin. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular, QT interval prolongation and 9.4 Drug-Drug Interactions.

Endocrine disorders: Hyperglycemia or glucose tolerance impaired has been reported in patients treated with methotrimeprazine maleate tablets. See 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism.

Gastrointestinal disorders: Dryness of the mouth. Chronic constipation, including paralytic ileus.

Patients should be advised of the risk of severe constipation during METHOPRAZINE treatment, and that they should tell their healthcare professional if constipation occurs or worsens, as they may need laxatives.

Necrotizing enterocolitis, which can be fatal, has been very rarely reported in patients treated with methotrimeprazine maleate tablets.

Hepatobiliary disorders: Rare cases of cholestatic jaundice and liver injury have been observed.

Investigations: Weight gain has been occasionally reported in patients during prolonged treatment with high doses. False positive pregnancy tests.

Metabolism and nutrition disorders: Hyponatremia, syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Nervous system disorders: Drowsiness may appear early in treatment but will gradually disappear during the first weeks or with an adjustment in the dosage. Cases of confusional states, delirium, and seizures have been reported. Phenothiazines, such as METHOPRAZINE, may impair sensitivity and adaptation to changes of environmental temperature, so that fatal hyperthermia and heat strokes are possible complications.

Extrapyramidal effects, including dystonias, akathisia, and parkinsonism are rare and usually appear only after prolonged therapy at high doses. These reactions may be corrected either by reducing the dose of METHOPRAZINE or by administering an antiparkinsonian agent.

As with other antipsychotic agents, tardive dyskinesia may occur in patients on long-term therapy and symptoms may persist long after therapy is discontinued or may be permanent, in some cases. The risk appears to be greater in children (including dystonias) and elderly patients. If the signs and symptoms of tardive dyskinesia appear during treatment, dosage reduction or discontinuation of METHOPRAZINE should be considered. Anticholinergic antiparkinsonian agents have no effect and may cause exacerbation. See 8.5 Post-Market Adverse Reactions.

Renal and urinary disorders: In older patients occasional urinary retention.

Reproductive system and breast disorders: Priapism has been very rarely reported. Altered libido, menstrual irregularities, lactation, inhibition of ejaculation, gynecomastia.

Skin and subcutaneous tissue disorders: Skin reaction, rash, photosensitivity reactions, pigmentation disorder are extremely rare.

Vascular disorders: Orthostatic hypotension may be encountered at the start of treatment with

high oral doses.

Cases of venous thromboembolism, including cases of pulmonary embolism, sometimes fatal, and cases of deep vein thrombosis have been reported with antipsychotic drugs. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular.

8.5 Post-Market Adverse Reactions

Blood and lymphatic system disorders:

- Leukopenia, eosinophilia, thrombocytopenia (including thrombocytopenic purpura).

Cardiac disorders:

- There have been reports of sudden death, with possible causes of cardiac origin as well as cases of unexplained sudden death, in patients receiving neuroleptic phenothiazines. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular.
- Torsades de pointes.
- ECG changes include QT prolongation (as with other neuroleptics), ST depression, U-Wave and T-Wave changes. Cardiac arrhythmias, including ventricular arrhythmias and atrial arrhythmias, atrioventricular block, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest have been reported during neuroleptic phenothiazine therapy, possibly related to dosage.

Endocrine disorders:

- Temperature regulation disorder, hyperprolactinemia which may result is galactorrhea, gynecomastia, amenorrhea, erectile dysfunction.

Eye disorders:

- Accommodation disorder, corneal deposits (brownish deposits in the anterior segment of the eye caused by accumulation of the drug and generally without effect on vision).

Immune System Disorders:

- Hypersensitivity, urticaria, angioedema.

Investigations:

- Positive serology for antinuclear antibodies without clinical lupus erythematosus.
- Liver function test abnormal.

Nervous system disorders:

- Parkinsonism.
- Dizziness, insomnia.
- Dystonia (spasmodic torticollis, oculogyric crises, trismus, etc.).
- Tardive dyskinesia occurring with long-term treatment. Tardive dyskinesia may occur after the neuroleptic agent is withdrawn and resolve after rechallenge or if the dose is increased. Anticholinergic antiparkinsonian agents have no effect and may cause exacerbation.

- Extrapyramidal syndrome: akinesia with or without hypertonia, partially relieved by anticholinergic antiparkinsonian agents, hyperkinetic-hypertonic movements, motor excitation, akathisia.
- Neuroleptic malignant syndrome. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX; 7 WARNINGS AND PRECAUTIONS, Neurologic, Neuroleptic malignant syndrome.
- Anticholinergic effects such as ileus paralytic, risk of accommodation disorders.

Pregnancy, puerperium and perinatal conditions:

- Drug withdrawal syndrome in neonatal. See 7.1.1 Pregnant Women.

Psychiatric disorders:

- Indifference, anxiety, mood altered.

Renal and urinary disorders:

- Risk of urinary retention.

Respiratory, thoracic and mediastinal disorders:

- Respiratory depression, nasal congestion.

Reproductive System and Breast Disorders:

- Ejaculation disorder.

Vascular disorders:

- Orthostatic hypotension.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- METHOPRAZINE is contraindicated in patients using concomitant neuroleptics including dopaminergics, due to mutual antagonism between dopaminergics and neuroleptics. See 2 CONTRAINDICATIONS and 9.4 Drug-Drug Interactions.
- Due to additive CNS depressant effect, the concomitant use of METHOPRAZINE and other phenothiazines or CNS depressants (e.g. barbiturates, analgesics, narcotics, sedatives, antihistaminics, antiepileptics, or general anesthetics) may result in respiratory depression. The usual doses of these agents should be reduced by half if they are to be given concomitantly with METHOPRAZINE until the dosage of the latter has been established. See 2 CONTRAINDICATIONS.

9.2 Drug Interactions Overview

Contraindicated combinations: METHOPRAZINE is contraindicated in patients using concomitant dopaminergics, due to mutual antagonism between dopaminergics and neuroleptics. Where treatment for neuroleptic-induced extrapyramidal symptoms is required, anticholinergic antiparkinsonian agents should be used in preference to levodopa, since neuroleptics antagonize the antiparkinsonian action of dopaminergics.

Dopaminergics may cause or exacerbate psychotic disorders. If treatment with neuroleptics is required in patients with Parkinson's disease treated with a dopaminergic, the latter should be tapered off gradually, as sudden discontinuation of dopaminergic agents exposes the patient to a risk of neuroleptic malignant syndrome (NMS). For parkinsonian patients who require treatment with both a neuroleptic and a dopaminergic agent, use the minimum effective doses of both medications.

Combinations not recommended or requiring precaution: The action of some drugs may be opposed by phenothiazine neuroleptics; these include amphetamine, clonidine, and adrenaline.

9.3 Drug-Behaviour Interactions

The CNS depressant actions of neuroleptic agents may be intensified (additively) by alcohol. Respiratory depression may occur. Impaired vigilance may make it dangerous to drive or use machines. Avoid consumption of alcoholic beverages and medications containing alcohol.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 2 - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
CYP2D6 substrate (e.g. Amitriptyline/ amitriptylinoxide)	T	Methotrimeprazine is a moderate inhibitor of CYP2D6. There is a possible pharmacokinetic interaction between inhibitors of CYP2D6, such as phenothiazines, and CYP2D6 substrates. Co-administration of methotrimeprazine with amitriptyline/amitriptylinoxide, a CYP2D6 substrate, may lead to an increase in the plasma levels of amitriptyline/amitriptylinoxide.	Monitor patients for dose-dependent adverse reactions associated with amitriptyline/ amitriptylinoxide.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Antidiabetic agents	T	Administration of METHOPRAZINE in patients taking antidiabetic agents can lead to an increase in blood sugar levels.	Forewarn the patient and advise increased self-monitoring of blood and urine levels. If necessary, adjust the antidiabetic dosage during and after discontinuing neuroleptic treatment.
Atropine and atropine-like substances	T	Cumulative adverse effects related to atropine-like substances such as urinary retention, constipation, dry mouth, etc.	Dosage adjustment may be necessary.
CNS depressant drugs (e.g. barbiturates, analgesics, narcotics, sedatives, antihistaminics)	T	Additive CNS depressant effects may result in respiratory depression.	The usual doses of CNS depressant drugs should be reduced by half if they are to be given concomitantly with METHOPRAZINE until the dosage of the latter has been established.
Gastro-intestinal agents that are not absorbed (magnesium, aluminium and calcium salts, oxides and hydroxides)	T	Reduced gastro-intestinal absorption of phenothiazine neuroleptics may occur.	Such gastro-intestinal agents should not be taken at the same time as phenothiazine neuroleptics (at least 2 hours apart, if possible).
Guanethidine	T	Inhibition of the antihypertensive effect of guanethidine.	Dosage adjustment may be necessary.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Lithium	T	Risk of developing neuropsychiatric symptoms suggestive of a neuroleptic malignant syndrome or of lithium poisoning.	Close monitoring is recommended.
Medicines that lower blood pressure	T	Enhanced antihypertensive effect and higher risk of postural hypotension (cumulative effects).	Dosage adjustment may be necessary.
Medicines that lower the seizure threshold		Potential for increased convulsive risks (cumulative effects)	Concomitant use should be carefully assessed.
Monoamine oxidase inhibitors	T	Potential for additive CNS and cardiovascular effects	METHOPRAZINE should be avoided in patients taking monoamine oxidase inhibitors within the previous 14 days, and monoamine oxidase inhibitors should be avoided while using METHOPRAZINE.

Proper/Common name	Source of Evidence	Effect	Clinical comment
QT prolonging drugs	T	There is an increased risk of arrhythmias when antipsychotics are used with concomitant QT prolonging drugs (including certain antiarrhythmics, antidepressants and other antipsychotics) and drugs causing electrolyte imbalance. Neuroleptic phenothiazines may potentiate QT interval prolongation. QT prolongation is exacerbated, in particular, in the presence of bradycardia, hypokalemia, and congenital or acquired (i.e., drug induced) QT prolongation (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).	If possible one of the two treatments should be discontinued.

T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

False positive or negative pregnancy tests have occurred in patients receiving phenothiazine therapy.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

METHOPRAZINE possesses antipsychotic, tranquilizing, anxiolytic, and analgesic properties.

METHOPRAZINE possesses strong sedative properties. It potentiates the pharmacological actions of anesthetics and opioids. It also exerts a potent anti-apomorphine effect, a hypothermic action 3 times more potent than that of chlorpromazine and strong antispasmodic

and anti-histaminic effects.

Methotrimeprazine maleate tablets is capable of reversing epinephrine-induced hypertension but has practically no effect against norepinephrine and acetylcholine. It readily protects rats against traumatic shock.

10.2 Pharmacodynamics

Information is not available.

10.3 Pharmacokinetics

Information is not available.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature 15°C to 30°C. Protect from light.

METHOPRAZINE should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

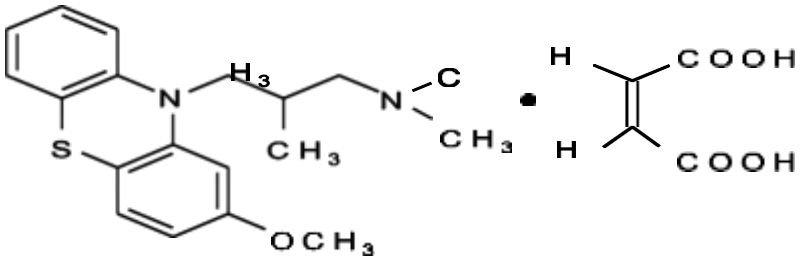
Non-proprietary name of the drug product: methotrimeprazine maleate

Chemical name: (1) 10*H*-phenothiazine-10-propanamine, 2-methoxy-*N,N,β*-trimethyl-, (-)-maleate

(2) (-)-10-[3-(dimethylamino)-2-methylpropyl]-2-methoxyphenothiazine maleate

Molecular formula and molecular mass: $C_{19}H_{24}N_2OS \bullet C_4H_4O_4$ and 444.6 g/mol

Structural formula:



Physicochemical properties: Methotrimeprazine is a fine, white, practically odorless, crystalline powder which melts at about 126°C. It is practically insoluble in water; freely soluble in chloroform and in ether; sparingly soluble in methanol. It is sparingly soluble in alcohol at 25°C, but is freely soluble in boiling alcohol.

14 CLINICAL TRIALS

14.2 Comparative Bioavailability Studies

A comparative bioavailability study was performed using healthy human volunteers. The rate and extent of absorption of methotrimeprazine were measured and compared following a single oral 25 mg dose of METHOPRAZINE or Nozinan. The results from measured data are summarized as follows:

Summary Table of the Comparative Bioavailability Data Methotrimeprazine Tablets (Dose: 25 mg) From Measured Data			
Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)
	METHOPRAZINE	Nozinan®†	
AUC_T (ng·hr/mL)	26.9 40.5 (87)	27.9 41.1 (80)	96.4
AUC_I (ng·hr/mL)	34.3 47.3 (82)	35.1 47.1 (73)	97.7
C_{max} (ng/mL)	3.44 4.66 (76)	3.67 4.96 (73)	93.7
T_{max} (h)*	2.96 (26)	2.73 (33)	--
$t_{1/2}$ (h)*	10.8 (49)	10.3 (49)	--
* Arithmetic means only (CV%). † Nozinan® (Rhône-Poulenc Rorer Inc.) was purchased at a Canadian retail pharmacy.			

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

In mice the LD_{50} of methotrimeprazine maleate is 70 mg/kg i.v., 250 mg/kg s.c., 344 mg/kg i.p. and 380 mg/kg p.o. Signs of acute toxicity consist of CNS depression interrupted by periods of convulsions and uncoordinated movements.

In the rat, a daily dose of 5 mg/kg or 10 mg/kg p.o. for 4 consecutive weeks did not produce any digestive troubles or weight loss. During the first days of treatment, a state of depression appeared, which was most pronounced on the third or fourth day and then almost completed disappeared. Laboratory and function tests indicated no renal, hepatic or blood anomalies. Microscopic visceral examinations revealed no toxic lesions.

In the dog, a daily dose of 2.5 mg/kg or 5 mg/kg p.o. for 4 consecutive weeks did not affect weight stability but animals appeared lethargic. Some relaxation of the nictitating membrane and a transient reduction of blood pressure were observed. During treatment, the leucocyte count and blood coagulation remained normal. Anatomopathological examination of the visceral parenchyma of sacrificed animals confirmed that all organs remain normal.

17 SUPPORTING PRODUCT MONOGRAPHS

1 NOZINAN®, Methotrimeprazine Hydrochloride Injection, 25 mg/mL, submission control: 279974, Product Monograph, Neuraxpharm Arzneimittel GmbH. (NOV 15, 2023).

2 NOZINAN®, Methotrimeprazine Maleate Tablets 5, 25, 50 mg and Methotrimeprazine Hydrochloride Injection, 25 mg/mL, submission control: 111761, Product Monograph, sanofi-aventis Canada Inc. (May 18, 2007)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]METHOPRAZINE

Methotrimeprazine Maleate Tablets

Read this carefully before you start taking **METHOPRAZINE** 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 **METHOPRAZINE**.

Serious Warnings and Precautions

Elderly Patients with Dementia: Medicines like METHOPRAZINE can raise the risk of death in elderly people who have dementia. METHOPRAZINE is not for use in patients with dementia.

Neuroleptic Malignant Syndrome (NMS): Rare, sometimes fatal cases of NMS (a type of disorder that affects the brain) have been reported in patients taking METHOPRAZINE. Symptoms may include muscle stiffness with a high fever, rapid or irregular heartbeat, sweating and confusion. If you think you are experiencing NMS, seek immediate medical help.

What is METHOPRAZINE used for?

METHOPRAZINE is used to treat:

- mental illnesses such as schizophrenia, disorders in the elderly, manic-depressive syndromes,
- pain due to cancer, shingles, trigeminal neuralgia, neurocostal neuralgia, phantom limb pains and muscular discomforts,
- nausea and vomiting,
- insomnia.

How does METHOPRAZINE work?

METHOPRAZINE is an antipsychotic medication which affects chemicals in the brain that allow communication between nerve cells (neurotransmitters). These chemicals are called dopamine and serotonin. Exactly how METHOPRAZINE works is unknown, but it seems to readjust the balance of dopamine and serotonin in your body.

What are the ingredients in METHOPRAZINE?

Medicinal ingredients: Methotrimeprazine Maleate

Non-medicinal ingredients: Carnauba wax, colloidal silicon dioxide, corn starch, d & c yellow #10 aluminum lake 14-18%, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sunset yellow aluminum lake 40% and titanium dioxide.

METHOPRAZINE comes in the following dosage forms:

Tablets: 2 mg, 5 mg, 25 mg and 50 mg

Do not use METHOPRAZINE if:

- you/your child are allergic to methotrimeprazine, phenothiazines (a type of antipsychotic) or to any of the other ingredients in METHOPRAZINE
- you/your child are in an altered state of consciousness or coma, due to alcohol, drugs that make you sleepy (hypnotic drugs), or pain medications
- you/your child are taking other drugs used to treat psychotic disorders including dopaminergics.
- you/your child have a blood disorder
- you/your child have a condition called bone marrow depression
- you/your child have liver problems
- you/your child have brain damage
- you/your child have a medical condition known as pheochromocytoma (a tumor of the adrenal gland)
- you/your child have a severe heart or blood vessel disorder
- you/your child have severely low blood pressure
- you/your child have a medical condition called myasthenia gravis (muscle weakness and fatigue)
- you/your child are going to receive anesthesia in the spine or for a large area of the body (such as an arm, leg or the lower part of your body)
- you/your child have urethra or prostate problems that may impact your/their ability to completely empty your/their bladder (urinary retention)
- you/your child are at risk for having glaucoma (increased pressure in the eye)

METHOPRAZINE is not for use in children less than 1 year of age.

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

- have heart or blood vessel disease.
- have a history of having strokes.
- suffer from an increase pressure within the eyes (glaucoma).
- suffer from an enlarged prostate (Benign Prostatic Hyperplasia) or prostatic hypertrophy.
- are addicted to alcohol. You should not take METHOPRAZINE if you are under the effects of alcohol.
- are pregnant, think you are pregnant or are of child-bearing potential and are not using effective birth control.
- have or have had seizure disorders (epilepsy).
- have kidney problems.
- have Parkinson's disease.
- have hypothyroidism (underactive thyroid gland).
- have heart failure (heart does not pump blood as well as it should).
- have heart problems or problems with your heart beat.
- have low levels of potassium in the blood.
- are taking any medications that affect how your heart beats.
- plan to have surgery.
- are breast feeding or are planning to breast feed.
- are at risk for developing blood clots or having a stroke; risk factors include:
    - a family history of blood clots or strokes
    - being over the age of 65,
    - smoking,
    - diabetes,
    - high cholesterol,
    - obesity,
    - recent major surgery (such as hip or knee replacement),
    - not being able to move due to air travel or other reason,
    - taking oral birth control (such as "The Pill").

Other warnings you should know about:

Do NOT stop taking METHOPRAZINE without talking to your healthcare professional first, as it may cause unwanted side effects such as headache, insomnia, numbness, tingling, burning, or prickling, nervousness, anxiety, nausea, sweating, dizziness, jitteriness and weakness.

Driving and using machines: Until you know how METHOPRAZINE affects you, do not drive or use machinery, especially when you first start treatment. Taking METHOPRAZINE can cause side effects such as:

- drowsiness,
- confusion,
- dizziness, and
- blurred vision.

Constipation: If you experience severe constipation and you are elderly, please consult your healthcare professional as soon as possible.

Monitoring and laboratory tests: Your healthcare professional should do tests before starting treatment with METHOPRAZINE and while you are taking it. These tests will monitor:

- blood sugar,
- body weight,
- blood count,
- liver and kidney,
- blood pressure, and
- if you/your child develop a sore throat, fever and weakness.

Increased levels of prolactin: METHOPRAZINE can raise the levels of a hormone called "prolactin". If you have high levels of prolactin (measured with a blood test) and a condition called hypogonadism you may be at increased risk of breaking a bone due to osteoporosis. This occurs in both men and women. High levels of prolactin may also impair fertility in both men and women.

Effects on Newborns: In some cases babies born to a mother taking METHOPRAZINE during pregnancy have experienced symptoms that are severe and require the newborn to be hospitalized. Sometimes, the symptoms may resolve on their own. Be prepared to seek immediate emergency medical attention for your newborn if they:

- have difficulty breathing,
- are overly sleepy,
- have muscle stiffness, or floppy muscles (like a rag doll),
- are shaking, or
- have difficulty feeding.

Dehydration and Overheating: It is important to not become too hot or dehydrated while you are taking METHOPRAZINE.

- Do not exercise too much,
- In hot weather, stay inside in a cool place if possible,
- Stay out of the sun,
- Do not wear too much clothing or heavy clothing,
- Drink plenty of water.

Sensitivity to sunlight: METHOPRAZINE may increase sensitivity to sunlight. You/your child should wear sunscreen if you/they will be spending time outside.

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

Serious Drug Interactions:

Do not use METHOPRAZINE if you/your child are taking:

- Other antipsychotic medications, including dopaminergic medications such as levodopa (often used to treat Parkinson's disease).
- Other phenothiazines, these are used to treat mental and emotional disorders.
- Central nervous system depressants such as:
  - barbiturates, used to relax the body and help with sleeping.
  - analgesics and narcotics, used to relieve pain.
  - sedatives, used to help with sleep.
  - antihistamines, used to treat allergies.
  - antiepileptics, used to control seizures or fits.
  - general anesthetics, used during surgery.

If you are unsure, ask your healthcare professional.

The following may interact with METHOPRAZINE:

- alcohol. METHOPRAZINE can add to the effects of alcohol. Avoid consuming alcoholic beverages while taking METHOPRAZINE.
- medicines used to treat heart rhythm problems, such as atropine.
- medicines used to treat depression, such as monoamine oxidase inhibitors, amitriptyline.
- medicines that lower the seizure threshold.
- medicines used to treat gastrointestinal problems, such as magnesium, aluminum and calcium salts, oxides and hydroxides.
- medicines used to treat diabetes.
- medicines used to lower blood pressure, such as guanethidine, guanadrel, bepridil, diltiazem, verapamil, beta blockers, clonidine, guanfacine.
- lithium, used in the treatment of mood disorders.
- adrenaline, a medicine used to treat life threatening allergic reactions.
- amphetamine, medicine used to treat Attention Deficit Hyperactivity Disorder (ADHD).

METHOPRAZINE may cause a false reading of some types of pregnancy tests. For more information, talk to your healthcare professional.

How to take METHOPRAZINE:

- Take this medication by mouth.

- Take exactly as your healthcare professional tells you to.
- During the first few days your healthcare professional may gradually increase your dose to allow your body to adjust to the medication.
- Do not take METHOPRAZINE more often than prescribed or increase your dose without consulting your healthcare professional. If you do, your condition will not improve any faster but the risk of serious side effects will be increased.
- Do not stop taking this drug suddenly without your healthcare professional's approval.

Usual dose:

Your healthcare professional will decide your/your child's dose of METHOPRAZINE and how often you/your child should take it. Take METHOPRAZINE exactly as your healthcare professional tells you to.

If you have any questions or concerns about your treatment, talk to your healthcare professional.

Overdose:

Overdose symptoms may include:

- agitation,
- confusion,
- drowsiness,
- dizziness,
- muscle stiffness or twitching,
- tremors (shaking),
- difficulty breathing,
- increased salivation,
- trouble swallowing,
- weakness,
- loss of balance or coordination,
- fainting,
- coma.

If you think you, or a person you are caring for, have taken too much METHOPRAZINE, contact a healthcare professional, hospital emergency department, or regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take your next dose at the regular time. Do not take extra medicine to

make up the missed dose.

What are possible side effects from using METHOPRAZINE?

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

Side effects may include:

- sweating
- leaking of urine due to loss of bladder control (urinary incontinence)
- inability to urinate
- dizziness
- drowsiness
- dry mouth
- nasal congestion
- nausea and vomiting
- headache
- sensitivity of the skin to the sun
- skin rash, hives
- menstrual changes
- change in libido
- impotence,
- swelling of the breasts and milk production in both men and women
- weight changes
- blurred vision
- anxiety or altered mood
- confusion
- insomnia (difficulty sleeping)
- changes in body temperature (feeling very hot and unable to cool down)
- severe constipation – if you become constipated while taking METHOPRAZINE tell your healthcare professional, you may need to take a laxative

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**	
COMMON			
Hypotension (low blood pressure): dizziness, fainting, light- headedness, blurred vision, nausea, vomiting, fatigue	√		

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	
(may occur when you go from lying or sitting to standing up)			
UNCOMMON			
Hyperglycemia (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision and fatigue		√	
Priapism: long-lasting (greater than 4 hours in duration) and painful erection of the penis			√
Respiratory depression (also known as hypoventilation): slow, shallow or weak breathing; blue lips, fingers, toes; confusion; headaches			√
Seizures (fit): uncontrollable shaking with or without loss of consciousness		√	
Tardive dyskinesia: muscle twitching or unusual/abnormal movement of the face or tongue or other parts of your body			√
Thromboembolism (blood clot in a vein or artery): pain or tenderness or swelling in your arm or leg, skin that is red or warm, coldness, tingling or numbness, pale skin, muscle pain or spasms, weakness			√
RARE			
Blood disorders (including agranulocytosis, neutropenia, granulocytopenia): abnormal blood cell count		√	
Extrapyramidal reactions: tremor, muscle stiffness, body spasm, impairment of voluntary			√

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	
movement, upward eye rolling, exaggeration of reflexes or drooling			
Heart rhythm problems: dizziness, light-headedness, shortness of breath, racing heart, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting or seizures			√
Jaundice: yellowing of the skin and eyes, dark urine, light coloured stool, itching all over your body		√	
VERY RARE			
Necrotizing enterocolitis (serious disease that affects the intestines): swelling, bloating in, or discolouration of the abdomen, bloody stool, diarrhea, vomiting			√
UNKNOWN			
Allergic reaction: difficulty swallowing or breathing, wheezing, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat			√
Hypertension (high blood pressure): headache, nausea, vomiting, shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations		√	
Hyperthermia (very high body temperature): severe muscle spasms, fast heart rate		√	

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**	
Hyponatremia (low blood sodium): lethargy, confusion, muscular twitching, achy, stiff or uncoordinated muscles, seizure, coma		√	
Neuroleptic malignant syndrome: pronounced muscle stiffness or inflexibility with high fever, rapid or irregular heartbeat, sweating, state of confusion or reduced consciousness			√
New or worsening constipation		√	
Paralytic ileus: abdominal pain or discomfort and constipation, due to inactive intestinal muscles		√	
SIADH—syndrome of inappropriate antidiuretic hormone secretion: concentrated urine (dark in colour), feel or are sick, have muscle cramps, confusion and fits (seizures) which may be due to inappropriate secretion of ADH (antidiuretic hormone)			√
Torsade de pointes (life-threatening irregular heartbeat)			√

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 healthcare 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 out of reach and sight of children.

If you want more information about METHOPRAZINE:

- 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); the manufacturer's website (https://www.aapharma.ca/en/), or by calling 1-877-998-9097.

This leaflet was prepared by AA Pharma Inc., Vaughan, Ontario, L4K 4N7.

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