Product Monograph

Including Patient Medication Information

[Pr]PERPHENAZINE

perphenazine tablets

For oral use

2 mg, 4 mg, 8 mg, and 16 mg

USP

Antipsychotic/Antiemetic

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Recent Major Label Changes

2. Contraindications	2026-05
4.1. Dosing Considerations	2026-05
7. Warnings and Precautions, General	2026-05
7. Warnings and Precautions, Cardiovascular	2026-05
7. Warnings and Precautions, Driving and Operating Machinery	2026-05
7. Warnings and Precautions, Endocrine and Metabolism	2026-05
7. Warnings and Precautions, Hematologic	2026-05
7. Warnings and Precautions, Monitoring and Laboratory Tests	2026-05
7. Warnings and Precautions, Neurologic	2026-05
7. Warnings and Precautions, Ophthalmologic	2026-05
7. Warnings and Precautions, Perioperative Considerations	2026-05
7. Warnings and Precautions, Renal	2026-05
7. Warnings and Precautions, Sensitivity/Resistance	2026-05
7. Warnings and Precautions, Skin	2026-05
7. Warnings and Precautions, 7.1.1. Pregnancy	2026-05
7. Warnings and Precautions, 7.1.2. Breastfeeding	2026-05
7. Warnings and Precautions, 7.1.4. Geriatrics	2026-05

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Recent Major Label Changes **2**

Table of Contents **2**

Part 1: Healthcare Professional Information **5**

1. Indications **5**

1.1. Pediatrics 5

1.2. Geriatrics 5

2. Contraindications **5**

3. Serious Warnings and Precautions Box **6**

4. Dosage and Administration 6
4.1. Dosing Considerations 6
4.2. Recommended Dose and Dosage Adjustment 7
4.4. Administration 7
4.5. Missed Dose 7
5. Overdose 7
6. Dosage Forms, Strengths, Composition, and Packaging 8
7. Warnings and Precautions 8
General 8
Cardiovascular 9
Dependence, Tolerance, and/or Abuse Liability 11
Driving and Operating Machinery 11
Endocrine and Metabolism 11
Gastrointestinal 11
Genitourinary 11
Hematologic 11
Hypotensive Effect of Perphenazine 12
Hepatic/Biliary/Pancreatic 12
Monitoring and Laboratory Tests 12
Neurologic 13
Ophthalmologic 14
Perioperative Considerations 14
Renal 14
Reproductive Health: Female and Male Potential 15
Sensitivity/Resistance 15
Skin 15
7.1. Special Populations 15
7.1.1. Pregnancy 15
7.1.2. Breastfeeding 15
7.1.3. Pediatrics 15
7.1.4. Geriatrics 16

8. Adverse Reactions 16
8.1. Adverse Reaction Overview 16
9. Drug Interactions **18**
9.1. Serious Drug Interactions 18
9.2. Drug Interactions Overview 18
9.3. Drug-Behaviour Interactions 19
9.4. Drug-Drug Interactions 19
9.5. Drug-Food Interactions 24
9.6. Drug-Herb Interactions 24
9.7. Drug-Laboratory Test Interactions 24
10. Clinical Pharmacology **24**
10.1. Mechanism of Action 24
10.2. Pharmacodynamics 25
10.3. Pharmacokinetics 25
11. Storage, Stability, and Disposal **25**
Part 2: Scientific Information **26**
13. Pharmaceutical Information **26**
14. Clinical Trials **26**
16. Non-Clinical Toxicology **26**
Patient Medication Information **27**

Part 1: Healthcare Professional Information

1. Indications

PERPHENAZINE (perphenazine tablets) is indicated for:

- Management of manifestations of psychotic disorders.
- Controlling nausea and vomiting due to stimulation of the chemoreceptor trigger zone.

PERPHENAZINE has not been shown effective for the management of behavioral complications in patients with intellectual developmental disorder.

1.1. Pediatrics

Pediatrics (<13 years of age): No data are available to Health Canada regarding use in children under 13 years of age; therefore, Health Canada has not authorized an indication for pediatric use in children under 13 years of age. See 7.1.3 Pediatrics and 4.1 Dosage Considerations.

1.2. Geriatrics

Geriatrics (>55 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 3 Serious Warnings and Precautions Box and 7.1.4 Geriatrics.

2. Contraindications

PERPHENAZINE is contraindicated in:

- Patients who are hypersensitive to this drug or to phenothiazine derivatives 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.
- Circulatory collapse, comatose, or greatly depressed states due to CNS depressant (including alcohol, hypnotics, narcotics).
- Blood dyscrasias and bone marrow depression.
- Liver damage.
- Patients with congenital long QT syndrome or with a family history of this syndrome and in patients with a history of cardiac arrhythmias or Torsade de Pointes. A pre-treatment ECG is thus recommended to exclude these conditions. PERPHENAZINE should not be used in the case of acquired long QT interval, such as associated with concomitant use of drugs known to prolong the QT interval (See 9.2 Drug Interactions Overview, Drugs that Prolong QT Interval), known hypokalemia or hypomagnesemia, or clinically significant bradycardia.
- Combination with serotonin reuptake inhibitors, such as citalopram. See 9.2 Drug Interactions Overview, SSRI (Selective Serotonin Reuptake Inhibitor) Antidepressants.
- Patients with pheochromocytoma, cerebrovascular or renal insufficiency, or severe cardiac reserve deficiency such as mitral insufficiency, as well as patients who have exhibited idiosyncrasy to other centrally-acting drugs may experience severe reactions to phenothiazine compounds and are particularly prone to hypotensive reactions. Patients with suspected or established subcortical brain damage, with or without hypothalamic damage, since a hyperthermic reaction with temperatures

above 40˚C may occur, sometimes not until 14 to 16 hours after drug administration.

- Patients receiving large doses of hypnotics, due to the possibility of potentiation.
- Patients with risk of urinary retention related to urethroprostatic disorders.
- Patients with risk of closed angle glaucoma.
- Concomitant use of dopaminergics. See 9.4 Drug-Drug Interactions, Cabergoline, Quinagolide.

3. Serious Warnings and Precautions Box

- **Increased Mortality in Elderly Patients with Dementia**

  Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo see 7.1.4 Geriatrics. PERPHENAZINE is not approved for use in elderly patients with dementia.

4. Dosage and Administration

4.1. Dosing Considerations

- Begin with the lowest recommended dosage.
- The dose must be adjusted for each patient according to the severity of the condition and the response obtained.
- The total daily dose in ambulatory patients should not exceed 24 mg.
- Severely disturbed hospitalized psychiatric patients or those with resistant mental and emotional disorders may temporarily require more than 24 mg daily, especially during early management.
- It is very important to employ the lowest effective dose since extrapyramidal symptoms increase in frequency and severity with increased dosage.
- For control of severe nausea and vomiting, daily doses of 8 mg to 16 mg may be given in divided amounts.
- All potential risk factors for venous thromboembolism (VTE) should be identified and preventative measures undertaken when prescribing PERPHENAZINE (See 7 Warnings and Precautions, Hematologic).
- Neutropenia, granulocytopenia and agranulocytosis have been reported during antipsychotic use. Therefore, it is recommended that patients have their complete blood count (CBC) tested prior to starting PERPHENAZINE and then periodically throughout treatment. See 7. Warnings and Precautions, Hematologic.
- Patients should have baseline and periodic monitoring of blood glucose and body weight. See 7. Warnings and Precautions, Monitoring and Laboratory Tests.
- **Debilitated patients:** Debilitated patients usually require a lower initial dose and more gradual dosage titration than do younger and healthier patients.
- **Geriatrics:** Geriatrics usually require a lower initial dose and more gradual dosage titration than do younger and healthier patients. Since they appear to be more susceptible to hypotension and neuromuscular reactions, such patients should be observed closely (see 7 Warnings and

Precautions, Neurologic).

- **Liver disease:** PERPHENAZINE is metabolized in the liver, dose reductions should be considered in patients with hepatic dysfunction.
- **Long-term therapy:** Prolonged administration of PERPHENAZINE at high dosages carries the risk of cumulative effects, with sudden onset of severe CNS or vasomotor symptoms. Periodic evaluations are recommended to assess continued dosage (see 7 Warnings and Precautions, General, Long-term therapy).

Children: (> 12 years of age)

- The lower range of adult dosage may be used in children over 12.

4.2. Recommended Dose and Dosage Adjustment

To treat psychotic disorders:

- Moderately disturbed non-hospitalized patients with schizophrenia:

  4 to 8 mg t.i.d. initially; reduce as soon as possible to minimum effective dosage.

- Hospitalized patients with schizophrenia:

  8 to 16 mg b.i.d. to q.i.d; avoid dosages in excess of 64 mg daily.

To control nausea and vomiting:

8 to 16 mg daily in divided doses; 24 mg occasionally may be necessary; early dosage reduction is desirable.

Pediatrics (<13 years of age)

Health Canada has not authorized an indication for pediatric use in children under 13 years of age.

4.4. Administration

Tablets are for oral administration.

4.5. Missed Dose

If a patient misses a dose, advise the patient to take the dose as soon as possible and continue with their regular schedule. If it is almost time for the next dose, advise the patient to skip the missed dose and continue with the next scheduled dose. Advise patients not to take 2 doses of PERPHENAZINE at the same time to make up for a missed dose.

5. Overdose

Symptoms

Primarily extrapyramidal reactions, CNS depression which may vary from simple lethargy to coma. Agitation and restlessness may also occur. Other possible manifestations include convulsions, fever and autonomic reactions such as hypotension, dry mouth and ileus.

Treatment

Essentially symptomatic and supportive. Early gastric lavage may be helpful.

Maintain an open airway If hypotension occurs, the standard measures for managing circulatory shock should be initiated; if a pressor agent is required give levarterenol or phenylephrine and not epinephrine as it may further depress the blood pressure. Extrapyramidal reactions should be treated with an antiparkinsonian agent.

Centrally-acting emetics will be ineffective because of perphenazine tablets antiemetic action. Limited experience indicates that phenothiazines are not dialyzable.

For the most recent information in the 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, and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet, 2 mg, 4 mg, 8 mg, and 16 mg of perphenazine	Carnauba wax, cornstarch, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide

Description

PERPHENAZINE 2 mg: Each white, round, biconvex, film-coated tablet engraved 2 on one side, other side plain, contains 2 mg of perphenazine. Available in bottles of 100.

PERPHENAZINE 4 mg: Each white, round, biconvex, film-coated tablet engraved 4 on one side, other side plain, contains 4 mg of perphenazine. Available in bottles of 100.

PERPHENAZINE 8 mg: Each white, round, biconvex, film-coated tablet engraved 8 on one side, other side plain, contains 8 mg of perphenazine. Available in bottles of 100.

PERPHENAZINE 16 mg: Each white, round, biconvex, film-coated tablet engraved 16 on one side, other side plain, contains 16 mg of perphenazine. Available in bottles of 100.

7. Warnings and Precautions

See 3 Serious Warnings and Precautions Box.

General

Patients receiving perphenazine tablets should be cautioned against organophosphorous insecticides.

- **Problematic Masking of nausea and vomiting as sign and symptom**

The antiemetic action of perphenazine tablets may mask the signs and symptoms of overdosage of other drugs and may obscure the diagnosis and treatment of other conditions such as brain tumour, intestinal obstruction and Reyes syndrome. Therefore the etiology of nausea and vomiting should be established before using the drug. (See 1.1. Pediatrics)

- **Prostatic hypertrophy:**

PERPHENAZINE should be avoided in prostate hypertrophy.

Because of its anticholinergic action, perphenazine tablets should be used with great caution in patients with prostatic hypertrophy.

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

- **Body Temperature Regulation:**

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Hyperpyrexia has been reported with other antipsychotic drugs. Appropriate care is advised when prescribing PERPHENAZINE to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity or being subject to dehydration.

- **Long-Term Therapy:**

With prolonged administration at high dosages, the possibility of cumulative effects, with sudden onset of severe CNS or vasomotor symptoms, should be kept in mind. To lessen the likelihood of adverse reactions related to cumulative drug effect , patients with a history of long-term therapy with PERPHENAZINE tablets and/or other antipsychotics, should be evaluated periodically to decide whether the maintenance dosage could be lowered or drug therapy discontinued

Patients on long-term phenothiazine therapy require regular and careful surveillance with particular attention to tardive dyskinesia and possible eye changes, blood dyscrasias, liver dysfunction and myocardial conduction defects, particularly if other concurrently administered drugs have potential effects in these systems.

Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore, a gradual withdrawal is advisable.

Cardiovascular

- **Potential for Hypotension:**

Hypotension may very rarely occur. Patients receiving PERPHENAZINE should be observed for evidence of hypotension. Some individuals, especially the elderly or debilitated, have demonstrated transient hypotension for several hours following drug administration.

Phenothiazines can produce alpha-adrenergic blockade. Because hypotension has occurred, large doses should be avoided in patients with impaired cardiovascular systems. To further minimize the occurrence of hypotension after initial administration, keep patient lying down and observe for at least 0.5 hour. If hypotension occurs, place patient in head-low position with legs raised. If a vasoconstrictor is required,

norepinephrine or phenylephrine is suitable. Other pressor agents, including epinephrine, should not be used as they may cause a paradoxical further lowering of blood pressure. See 5 Overdose.

- **Anginal Pain:**

PERPHENAZINE therapy may produce an increase in mental and physical activity. In certain instances, this effect may not be desirable. For example, some patients with angina pectoris have complained of increased pain while taking PERPHENAZINE tablets; therefore, if PERPHENAZINE is used in angina patients, such patients should be observed carefully and if an unfavourable response is noted, the drug should be withdrawn.

- **Prolongation of QT Interval:**

PERPHENAZINE is contraindicated in patients with a family history of QT prolongation; therefore, avoid concomitant use with QT prolonging drugs. Use with caution in patients with cardiovascular disease. See 2 Contraindications.

Particular care should be exercised when administering PERPHENAZINE or its use avoided in patients who are suspected to be at an increased risk of experiencing Torsade de Pointes during treatment with a QT/QTc-prolonging drug. See 2 Contraindications. Risk factors for Torsade de Pointes in the general population include, but are not limited to, the following:

- female
- age 65 years or older
- baseline prolongation of the QT/QTc interval
- presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes
- family history of QT prolongation, or sudden cardiac death at <50 years
- cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, left ventricular hypertrophy, cardiomyopathy, conduction system disease)
- history of arrhythmias (especially ventricular arrhythmias, atrial fibrillation, or recent conversion from atrial fibrillation)
- electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia)
- bradycardia
- acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma)
- hepatic dysfunction, renal dysfunction, and/or phenotypic/genotypic poor metabolizers of drug metabolizing enzyme isoforms, if relevant to the elimination of the drug
- diabetes mellitus
- nutritional deficit
- autonomic neuropathy

Physicians who prescribe drugs that prolong the QT/QTc interval should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the

drug.

Dependence, Tolerance, and/or Abuse Liability

Sudden discontinuance in long-term psychiatric patients may cause temporary symptoms, e.g., nausea and vomiting, dizziness, tremulousness.

Withdrawal Emergent Neurological Signs: Abrupt withdrawal after short-term administration of antipsychotic drugs does not generally pose problems. However, transient dyskinetic signs are experienced by some patients on maintenance therapy after abrupt withdrawal. The signs are very similar to those described under Tardive Dyskinesia, except for duration. Although it is not known whether gradual withdrawal of antipsychotic drugs will decrease the incidence of withdrawal emergent neurological signs, gradual withdrawal would appear to be advisable.

Driving and Operating Machinery

The use of PERPHENAZINE may impair the mental and physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery.

Potentiation of the effects of alcohol may also occur.

Administer the phenothiazine cautiously, forewarn the patient, and increase the dosage gradually.

Endocrine and Metabolism

Hyperglycemia: 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:

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration and may cause galactorrhoea, gynecomastia, oligomenorrhea or amenorrhoea, and erectile dysfunction. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone mineral density in both female and male subjects.

Gastrointestinal

The effects of anticholinergic drugs may be potentiated by perphenazine tablets. Paralytic ileus, even resulting in death, may occur, especially in the elderly. Caution should be observed if constipation develops.

Genitourinary

Rare cases of priapism have been reported with antipsychotic use, such as perphenazine 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.

Hematologic

Blood Dyscrasias: Blood dyscrasias including leukopenia, agranulocytosis, pancytopenia,

thrombocytopenic or non- thrombocytopenic purpura, eosinophilia, and anemia, have been associated with phenothiazine therapy. Routine blood counts are therefore advisable during prolonged therapy. If any soreness of the mouth, gums or throat or any symptoms of upper respiratory infection occur and confirmatory leukocyte count indicates cellular depression, therapy should be discontinued and other appropriate measures instituted immediately.

Patients who have experienced blood dyscrasias (agranulocytosis, anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia) or bone marrow suppression with a phenothiazine should not be re-exposed to any phenothiazine, including PERPHENAZINE tablets unless in the judgement of the healthcare professional the potential benefits of treatment outweigh the possible hazards, (see 4. Dosage and Administration, 4.1. Dosing Considerations).

Venous Thromboembolism (VTE): Cases of venous thromboembolism (VTE), including fatal pulmonary embolism, have been reported with antipsychotic drugs.

Hypotensive Effect of Perphenazine

Patients with pheochromocytoma, cerebral vascular or renal insufficiency, or a severe cardiac reserve deficiency such as mitral insufficiency appear to be particularly prone to hypotensive reactions with phenothiazine compounds and should therefore be observed closely when the drug is administered. Hypotension severe enough to cause fatal cardiac arrest has been reported in patients receiving phenothiazine derivatives

Should hypotension occur in patients receiving Perphenazine and a vasopressor agent be required, i.v. levarterenol or phenylephrine should be used, and not epinephrine, since phenothiazine derivatives can reverse the pressor effect of the latter drug.

Hepatic/Biliary/Pancreatic

Cholestatic jaundice may occur with long-term therapy, necessitating discontinuation of treatment Therefore, it is advisable to perform periodic liver function tests, particularly during the first 2 or 3 months.

Monitoring and Laboratory Tests

Phenothiazines may result in falsely positive or negative pregnancy test results due to interference based on immunological reactions between human chorionic gonadotropin (HCG) and anti-HCG.

The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

Assess blood glucose and body weight at baseline and monitor them at appropriate intervals during therapy.

A complete blood count (CBC) should be obtained at baseline and monitored periodically throughout treatment.

White blood cell (WBC) and differential counts, as well as liver function tests, should be monitored periodically during therapy.

Sore throat, fever, or weakness in patients receiving prolonged therapy may be indicative of agranulocytosis. If these symptoms occur, discontinue treatment and perform appropriate laboratory evaluation, including liver function tests.

Renal function should be monitored in patients receiving prolonged therapy. If abnormal renal

parameters are observed, discontinue treatment.

Neurologic

Extrapyramidal Symptoms: In common with all neuroleptics, extrapyramidal symptoms may occur. See 8.1 Adverse Reaction Overview, Nervous system disorders.

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex, sometimes referred to as Neuroleptic Malignant Syndrome (NMS), has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, generalised muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Patients with Parkinson's disease or dementia may be at increased risk. Hyperthermia is often an early sign of this syndrome. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. 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 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 reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Seizures: The increased incidence of seizures, which occasionally occur in epileptics started on antipsychotic medication, may be controlled by increasing the dosage of their anticonvulsant. Patients with a familial history of seizures or febrile convulsions are more likely to develop seizures than those who have no such history.

Unexpected, sudden deaths have occurred in hospitalized patients treated with phenothiazines. Previous brain damage or seizures may predispose. High doses of perphenazine should be avoided in known seizure patients. See 8.1 Adverse Reaction Overview, General disorders and administration site conditions

Tardive dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome 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 effective treatment for tardive dyskinesia; antiparkinsonian agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. It has been reported that the fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time, the syndrome may not develop. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, and thereby may possibly mask the underlying disease process; this includes from increased dosage, reinstated treatment, or switch to a different antipsychotic agent. The effect that symptomatic suppression has upon the long- term course of the syndrome is unknown.

Given these considerations antipsychotics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

Ophthalmologic

Phenothiazines have been reported to produce retinopathy, especially with long-term treatment at high dosage.. Should ophthalmoscopic examination or visual field studies demonstrate retinal changes in patients on perphenazine tablets, the drug should be discontinued.

The possibility of persistent tardive dyskinesia should also be borne in mind when patients are under long-term treatment.

Angle-Closure Glaucoma: As with other antipsychotics, PERPHENAZINE can cause mydriasis, which may trigger an angle-closure attack in a patient with anatomically narrow ocular angles. Healthcare professionals should inform patients to seek immediate medical assistance if they experience eye pain, changes in vision or swelling or redness in or around the eye.

Because of its anticholinergic effect or cause mydriasis, perphenazine should be used with great caution in patients with glaucoma. (see 2. Contraindications)

Perioperative Considerations

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 anaesthetics or CNS depressants may be required.

Renal

Renal dysfunction has been observed with perphenazine use. Therefore, renal function should be monitored and, if BUN becomes abnormal, treatment should be discontinued. Patients who may develop urinary retention should be carefully observed. This drug should not be used in patients with renal insufficiency.

Reproductive Health: Female and Male Potential

- **Teratogenic Risk:**

Non-Teratogenic Effects: Neonates exposed to antipsychotic drugs (including perphenazine tablets) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. 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. Consequently, newborns should be monitored carefully.

Sensitivity/Resistance

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Skin

Skin pigmentation have been reported in a few hospitalized mental patients taking substantial doses of some phenothiazine derivatives for prolonged periods. Present evidence suggests that these changes may be reversible.

7.1. Special Populations

7.1.1. Pregnancy

Safety during pregnancy has not been established. Therefore, it is recommended that the drug be given to pregnant patients only when, in the judgement of the physician, the potential benefit to the patient outweighs the possible risk to the fetus.

When given in high doses during late pregnancy, phenothiazines have caused prolonged extrapyramidal disturbances in the child. There are also reports of prolonged jaundice and hyperreflexia or hyporeflexia in newborn infants whose mothers received phenothiazines.

PERPHENAZINE should not be used during pregnancy unless the expected benefits to the mother markedly outweigh the potential risks to the fetus.

7.1.2. Breastfeeding

There is evidence that phenothiazines are excreted in the milk of nursing mothers.

It is unknown if perphenazine tablets are excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk.

7.1.3. Pediatrics

Pediatrics (< 13 years of age): No data are available to Health Canada regarding use in children under 13 years of age; therefore, Health Canada has not authorized an indication for pediatric use in children under 13 years of age. See 1.1 Pediatrics.

Children with an acute febrile illness or suffering from dehydration seem to be much more susceptible than adults to neuromuscular reactions, particularly dystonias. In such patients, the drug should be used under close supervision and at low doses.

The extrapyramidal symptoms which can occur secondary to perphenazine tablets may be confused with the CNS signs of an undiagnosed primary disease responsible for the vomiting, e.g. Reye's syndrome or other encephalopathy. The use of perphenazine tablets should be avoided in children and adolescents whose signs and symptoms suggest Reye's syndrome.

7.1.4. Geriatrics

Geriatrics (>55 years of age): The incidence of adverse reactions may be greater in patients over 55 years of age, since the half-lives of antipsychotic drugs are often prolonged. To minimize this possibility, the maintenance dosage should be reduced to the lowest effective level as soon as possible after initial titration and periodically reviewed.

Since psychiatric syndromes in the elderly can be caused by drugs or organic disease, withdrawal of the precipitating drug or treatment of the medical condition should supersede initiation of antipsychotic medication. These agents should not be used for non-psychiatric conditions for which other drugs are available, since the elderly are especially prone to develop adverse effects from antipsychotic drugs.

Use in Geriatrics with Dementia

Overall Mortality

PERPHENAZINE is not indicated for the treatment of elderly patients with dementia.

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. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

Observational studies suggest that, similar to atypical antipsychotic drugs, 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.

8. Adverse Reactions

8.1. Adverse Reaction Overview

Adverse reactions 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 reactions may be more likely to occur with greater intensity, in patients with special medical problems.

Not all of the following adverse reactions have been observed 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.

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

Blood and lymphatic system disorders: Neutropenia, granulocytopenia and agranulocytosis have been reported during antipsychotic use. See 7 Warnings and Precautions, Blood Dyscrasias.

Cardiac disorders: Tachycardia.

Eye disorders: Glaucoma, blurred vision.

Epithelial keratopathy, lenticular and corneal deposits have been associated with long-term administration in patients receiving phenothiazine derivatives.

Gastrointestinal disorders: Dry mouth, nausea, constipation, vomiting have been observed.

Other autonomic reactions which have occurred with phenothiazines are salivation, adynamic ileus, and fecal compaction.

General disorders and administration site conditions: Disturbed temperature regulation, fatigue, peripheral edema.

Hyperpyrexia has been reported in patients receiving phenothiazine derivatives.

Sudden, unexpected and unexplained deaths have been reported in hospitalized psychotic patients receiving phenothiazines. Previous brain damage or seizures may be predisposing factors; high doses should be avoided in known seizure patients. Several patients have shown flare-ups of psychotic behaviour patterns shortly before deaths. Autopsy findings have usually revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents or intramyocardial lesions. See 7 Warnings and Precautions, Seizures.

Potentiation of CNS depressants (barbiturates, narcotics, analgesics, alcohol, antihistamines) may occur.

Hepatobiliary disorders: Cholestatic jaundice and biliary stasis may be encountered, particularly during the first months of therapy, and require immediate discontinuation of treatment.

Immune system disorders: The possibility of an anaphylactoid reaction should be borne in mind.

Investigations: Weight changes, false positive pregnancy tests, altered cerebrospinal fluid proteins, ECG and EEG changes have been reported in patients receiving phenothiazine derivatives.

Metabolism and nutrition disorders: Anorexia, increased thirst, increased appetite have occurred in patients receiving phenothiazine therapy.

Musculoskeletal and connective tissue disorders: Systemic lupus erythematosus-like syndrome, has been reported in patients receiving phenothiazine derivatives.

Nervous system disorders: Headache, syncope, dizziness have been observed.

Cerebral and angioneurotic edema has been reported in patients receiving phenothiazine derivatives.

Extrapyramidal reactions including tremor, rigidity, akathisia, dystonia, dyskinesia, oculogyric crises, opisthotonos, hyperreflexia and sialorrhea. Seizures have also been encountered.

Persistent Tardive Dyskinesia (see also 7 Warnings and Precautions, Tardive Dyskinesia)

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs, including perphenazine. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes, these may be accompanied by involuntary movements of the extremities. The physician may be able to reduce the risk of this syndrome by minimizing the unnecessary use of neuroleptic drugs and reducing the dose or discontinuing the drug, if possible, when manifestations of this syndrome are recognized, particularly in patients over the age of 50.

Neuroleptic Malignant Syndrome (see also 7 Warnings and Precautions, Neuroleptic Malignant Syndrome)

As with other neuroleptic drugs, a symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) may occur. Cardinal features of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs), and evidence of autonomic instability (irregular pulse or blood pressure). Additional signs may include elevated CPK, myoglobinuria (rhabdomyolysis), and acute renal failure. NMS is potentially fatal and requires symptomatic treatment and immediate discontinuation of neuroleptic treatment.

Psychiatric disorders: Sleep disturbances, drowsiness, insomnia, and depression have been reported and may, in severe cases, necessitate reduction in dosage. As with other phenothiazine derivatives, reactivation or aggravation of psychotic processes may be encountered. Paradoxical effects such as agitation, anxiety, restlessness, excitement and bizarre dreams, have been observed.

Renal and urinary disorders: Polyuria, bladder paralysis, urinary incontinence.

Reproductive system and breast disorders: Menstrual irregularities, impotence, galactorrhea, gynecomastia and changes in libido have also occurred in patients receiving phenothiazine therapy.

Respiratory thoracic and mediastinal disorders: Nasal congestion has been observed. Asthma and laryngeal edema have been reported in patients receiving phenothiazine derivatives.

Skin and subcutaneous tissue disorders: Pruritus, dermatitis, rash, erythema, urticaria, seborrhea, eczema, exfoliative dermatitis and photosensitivity.

Sweating has been observed. Skin pigmentation has been associated with long-term administration in patients receiving phenothiazine derivatives.

Vascular disorders: Observational studies and/or case reports of venous thromboembolism (VTE), including fatal pulmonary embolism, have been reported with antipsychotic drugs, including perphenazine tablets. (See 7 Warnings and Precautions, Venous Thromboembolism (VTE)).

9. Drug Interactions

9.1. Serious Drug Interactions

- **Drugs that Prolong QT Interval:** Concomitant use of PERPHENAZINE tablets with drugs known to prolong the QT interval are contraindicated. See 2 Contraindications and 9.2 Drug Interactions Overview, Drugs that Prolong QT Interval.
- **Selective Serotonin Reuptake Inhibitors:** PERPHENAZINE is contraindicated in combination with serotonin reuptake inhibitors, such as citalopram. See 2 Contraindications and 9.2 Drug Interactions Overview, SSRI (Selective Serotonin Reuptake Inhibitor) Antidepressants.
- **Dopaminergics**: PERPHENAZINE is contraindicated in combination with dopaminergics, such as Cabergoline and Quinagolide. See 2 Contraindications, and 9.4 Drug-Drug Interactions.

9.2. Drug Interactions Overview

Potentiation may happen with CNS depressants such as alcohol, hypnotics, anaesthetics and strong analgesics, or with antihypertensives or other drugs with hypotensive activity, anticholinergics or antidepressants.

Drugs that Prolong QT Interval

Concomitant use of PERPHENAZINE tablets with drugs known to prolong the QT interval are contraindicated. See 2 Contraindications.

Drugs that have been associated with QT/QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QT/QTc prolongation and/or torsade de pointes:

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide)
- Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide)
- antipsychotics (e.g., chlorpromazine, pimozide, droperidol)
- antidepressants (e.g., fluoxetine, venlafaxine, tricyclic/tetracyclic antidepressants)
- opioids (e.g., methadone)
- macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin)
- quinolone antibiotics (e.g., moxifloxacin)
- pentamidine
- antimalarials (e.g., quinine)
- azole antifungals (e.g., fluconazole, itraconazole, ketoconazole, voriconazole)
- domperidone
- tacrolimus
- 5-HT3 antagonists (e.g., dolasetron, ondansetron)
- beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol)

Particular care should be taken to avoid toxic plasma levels of lithium when this agent is administered together with PERPHENAZINE, since such toxic levels have also been associated with QT prolongation.

Do not administer in combination with drugs causing electrolyte alteration. Concomitant use with diuretics should be avoided, in particular those causing hypokalemia.

SSRI (Selective Serotonin Reuptake Inhibitor) Antidepressants

Combination with serotonin reuptake inhibitors, such as citalopram may result in an increased risk of QT interval prolongation.

9.3. Drug-Behaviour Interactions

Potentiation of the effects of alcohol may also occur. See 7 Warnings and Precautions, Driving and Operating Machinery.

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

Non-proprietary names of the drug products	Source of evidence	Effect	Clinical comment
Antacids		Antacids can reduce the absorption of	For better results and to avoid harmful

Non-proprietary names of the drug products	Source of evidence	Effect	Clinical comment
		phenothiazines.	interactions, antacids are prescribed before or after two hours taking any medication.
Anticholinergics (muscle relaxants)		Phenothiazines have mild anticholinergic activity which may be enhanced by other anticholinergic drugs. Anticholinergic drugs may decrease the antipsychotic effect of phenothiazines.	Dosage adjustment may be necessary.
Anticonvulsants	T	Phenothiazines may lower the convulsive threshold. Potentiation of anticonvulsant effects does not occur. However, it has been reported that phenothiazines may interfere with the metabolism of phenytoin and thus precipitate phenytoin toxicity	Dosage adjustment of anticonvulsants may be necessary.
Antihypertensives	T	Antipsychotics, notably the phenothiazines, have blocked the action of antihypertensive agents.	Concomitant administration of antihypertensive agents should be undertaken with caution
Atropine and atropine-like substances	T	Phenothiazines may potentiate the effect of atropine. Cumulative adverse effects related to atropine-like substances such as urinary retention, constipation, dry mouth, etc.	Dosage adjustment may be necessary.
Cabergoline, Quinagolide	T	Dopaminergics (cabergoline, quinagolide), not including dopaminergic antiparkinsonism agents, are contraindicated: reciprocal	If treatment with neuroleptics is required in patients with Parkinson's Disease treated with

Non-proprietary names of the drug products	Source of evidence	Effect	Clinical comment
		antagonism of the dopaminergic agent and neuroleptic.	dopaminergics, the latter should be tapered off gradually, as sudden discontinuation of dopaminergic agents exposes the patient to a risk of NMS.
Dantrolene (calcium channel blocker, muscle relaxant)	T	Drowsiness may occur with dantrolene sodium therapy, and the concomitant administration of CNS depressants such as sedatives and tranquilizing agents may result in further drowsiness.	Dosage adjustment may be necessary. Caution should be exercised in the concomitant administration of tranquilizing agents.
Epinephrine	T	Phenothiazines may reverse epinephrine's action and thereby cause a further fall in blood pressure.	Avoid epinephrine in the treatment of phenothiazine induced hypotension.
Guanethidine Guanadrel	T	Antihypertensive effects of guanethidine and related compounds may be counteracted when phenothiazines are used concurrently (inhibition of guanethidine, guanadrel uptake into sympathetic fibre, its site of action).	Combination of guanethidine, or guanadrel with phenothiazines should be taken into consideration.
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).
Lithium		Encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis,	The combination of lithium and PERPHENAZINE should only be used with extreme caution.

Non-proprietary names of the drug products	Source of evidence	Effect	Clinical comment
		elevated serum enzymes, BUN and FBS), and neurotoxicity, with sleep walking has occurred in a few patients treated with lithium plus a neuroleptic. In some instances, the syndrome was followed by irreversible brain damage. It has also been noted that serum levels of phenothiazines can be reduced to non-therapeutic concentrations by concurrent lithium administration. This encephalopathic syndrome may be similar to or the same as neuroleptic malignant syndrome (NMS).	Because of a possible causal relationship between these events and the concomitant administration of lithium and neuroleptics, patients receiving such combined therapy should be monitored closely for early evidence of neurologic toxicity and treatment discontinued promptly if such signs appear.
Oral anticoagulants	T	Phenothiazines may diminish the effect of oral anticoagulants.	Monitor INR levels closely during initiation and discontinuation of PERPHENAZINE. Consider dose adjustment of the anticoagulant based on INR levels.
Hormonal contraceptives	T	Estrogen potentiates the hyperprolactinemia effect of phenothiazines.	Dosage adjustment may be necessary. If galactorrhea or hyperprolactinemia occurs, use other non-hormonal method of contraception.
Organophosphate insecticides	T	Phenothiazines may potentiate the effect of organophosphate insecticides.	Dosage adjustment may be necessary.
Propranolol	T	Concomitant administration of propranolol with phenothiazines results in increased plasma levels of	This may lead to an enhanced antipsychotic effect of PERPHENAZINE and an

Non-proprietary names of the drug products	Source of evidence	Effect	Clinical comment
		both drugs.	increased antihypertensive effect of Propranolol.
Sedatives, narcotics, anesthetics, tranquilizers, barbiturates, opiates, and other CNS depressants.	T	Phenothiazines may increase the effects of general anesthetics, opiates, barbiturates, and other CNS depressants If agents such as sedatives, narcotics, anesthetics, tranquilizers are used either simultaneously or successively with PERPHENAZINE, the possibility of an undesirable additive depressant effect should be considered. Phenothiazines may increase the effects of general anesthetics, opiates, barbiturates, alcohol and other CNS depressants. Other CNS depressants include morphine derivatives (analgesics, antitussives and substitution treatments), barbiturates, benzodiazepines, anxiolytics other than benzodiazepines, hypnotics, sedative antidepressants, histamine H1 receptor antagonists, central antihypertensive agents increased central depression. Changes in alertness can make it dangerous to drive or operate machinery.	Dosage reduction may be necessary if administered concomitantly with perphenazine tablets.
Thiazide diuretics	T	Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines.	Blood pressure should be monitored during concomitant use of thiazide diuretics and phenothiazines.
Tramadol	T, C	Increased risk of seizures.	Caution should be used

Non-proprietary names of the drug products	Source of evidence	Effect	Clinical comment
		Seizures have been reported in patients using tramadol.	if tramadol is to be administered to patients receiving neuroleptic therapy. If possible, avoid this combination, especially in patients with underlying conditions that might predispose to seizures.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5. Drug-Food Interactions

Interactions with food have not been established.

9.6. Drug-Herb Interactions

Betel Nut: Case reports have described increased extrapyramidal side effects when betel nut (or areca nut) was chewed by patients taking fluphenazine or fluphenthixol for schizophrenia. The extrapyramidal effects were not improved with anticholinergic therapy with procyclidine, and resolved with betel nut discontinuation.

The cholinergic activity of betel nut has been attributed to the arecoline content. When given with peripheral anticholinergics, arecoline increased the heart rate due to central muscarinic agonist activity. Case reports suggest the onset of betel nut activity to be within 2 weeks with resolution within 4 to 7 days after discontinuation.

9.7. Drug-Laboratory Test Interactions

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Phenothiazines may result in falsely positive or negative pregnancy test results due to interference based on immunological reactions between human chorionic gonadotropin (HCG) and anti-HCG.

The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

10. Clinical Pharmacology

10.1. Mechanism of Action

Perphenazine is a piperazine phenothiazine derivative with antipsychotic, antiemetic and weak sedative activity.

10.2. Pharmacodynamics

Perphenazine has actions similar to those of other phenothiazine derivatives but appears to be less sedating and to have a weak propensity for causing hypotension or potentiating the effects of CNS depressants and anesthetics. However, it produces a high incidence of extrapyramidal reactions.

10.3. Pharmacokinetics

Absorption

Perphenazine is well absorbed from the gastrointestinal tract. Onset of action following oral administration is 30 to 40 minutes. Duration of action is 3 to 4 hours.

Distribution

Perphenazine distributes to most body tissues with high concentrations being distributed into liver and spleen.

Metabolism

Perphenazine enters the enterohepatic circulation.

Elimination

Perphenazine is excreted chiefly in the feces.

11. Storage, Stability, and Disposal

Store at controlled room temperature (between 15 to 30°C).

Part 2: Scientific Information

13. Pharmaceutical Information

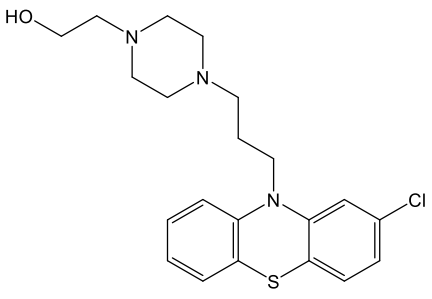
Drug Substance

Non-proprietary name of the drug substance: Perphenazine

Chemical name: 2-[4-[3-(2-chlorophenothiazin-10-yl)propyl]piperazin-1-yl]ethanol.

Molecular formula and molecular mass: $C_{21}H_{26}ClN_3OS$ and 404.0 g/mol.

Structural formula:



Physicochemical properties:

Appearance: A white or yellowish-white crystalline powder.

Solubility: Practically insoluble in Water, freely soluble in Methylene Chloride, soluble in Ethanol (96%). It dissolves in dilute solutions of Hydrochloric Acid.

pKa: 7.8

Potential Isomerism/Chirality: No chiral centres are present in perphenazine. No other form of isomers is possible.

Polymorphism: Perphenazine has been reported to exist in multiple polymorphic forms. However, the exact number of polymorphs can vary depending on the conditions under which the drug is crystallized. The most stable polymorph of perphenazine is the triclinic form. This form is considered the most stable at room temperature, making it the preferred choice for pharmaceutical formulations due to its consistent solubility and bioavailability.

14. Clinical Trials

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

16. Non-Clinical Toxicology

This information is not available for this drug product.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]PERPHENAZINE

perphenazine tablets

This Patient Medication Information is written for the person who will be taking **PERPHENAZINE**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **PERPHENAZINE**, talk to a healthcare professional.

Serious warnings and precautions box

- PERPHENAZINE belongs to a group of medicines called antipsychotics. These medicines have been linked to a higher rate of death when used in elderly patients with dementia (loss of memory and other mental abilities).
- PERPHENAZINE is **not** to be used if you are elderly and have dementia.

What PERPHENAZINE is used for:

PERPHENAZINE is used in adults and children (over 12 years of age) to:

- manage the symptoms of psychotic disorders.
- control nausea and vomiting

How PERPHENAZINE works:

PERPHENAZINE belongs to a class of medicines known as antipsychotics. The exact way PERPHENAZINE works is not known. However, it is thought to re-adjust the balance of certain chemicals in the brain (i.e., dopamine and serotonin) that allow communication between nerve cells.

The ingredients in PERPHENAZINE are:

Medicinal ingredient: Perphenazine

Non-medicinal ingredients: Carnauba wax, cornstarch, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

PERPHENAZINE comes in the following dosage form:

Tablets: 2 mg, 4 mg, 8 mg and 16 mg.

Do not use PERPHENAZINE if:

- you are allergic to perphenazine, phenothiazines (a group of antipsychotic medications), or to any of the other ingredients in PERPHENAZINE.
- you are in a deep state of prolonged unconsciousness (coma) or have decreased alertness caused by certain medications or alcohol.
- you have a blood cell disorder (e.g., low levels or red or white blood cells, or platelets).
- you have bone marrow depression (a condition where the bone marrow does not make enough blood cells and platelets).
- you have or have a family history of long QT syndrome (a heart rhythm condition that causes fast, chaotic heartbeats) or develop this syndrome during your treatment with PERPHENAZINE.
- you have or have had a condition that causes you to have an abnormal heart rhythm (e.g., Torsade de Pointes, atrial fibrillation, low heart rate).
- you take any medications that affect how your heart beats. For example:
  - medicines used to treat an abnormal heart rhythm.
  - antidepressant medications known as Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g., citalopram).
  - any medications that can cause an electrolyte imbalance (e.g., diuretics, also known as "water pills").
- you have a medical condition known as pheochromocytoma (a tumor of the adrenal gland).
- you have a severe heart or blood vessel problems.
- you have liver or kidney problems.
- you have or have had brain damage.
- you are taking hypnotics (medicines used to help with sleep).
- you are at risk for urinary retention due to disorders of the urethra or prostate.
- you are at risk of having glaucoma (increased pressure in the eye).
- are taking medicines known as dopaminergics.

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

- are currently taking any other medications.
- have a condition that affects your heart and blood vessels.
- have or are prone to low blood pressure.
- have chest pain (angina pectoris)
- suffer from an increased pressure within the eye(s) (glaucoma).
- are addicted to alcohol. You should not take PERPHENAZINE if you are under the effects of alcohol.
- are receiving or planning to receive anesthesia (medicines used to induce sleep and prevent pain during surgery).
- have seizures, epilepsy, abnormal electrical activity in the brain or brain damage. PERPHENAZINE may make you more prone to seizures.
- are at risk for Torsade de Pointes (a heart rhythm condition). Risk factors include, but are not limited to:
  - being female.
  - being 65 years of age or older.
  - being genetically predisposed for heart rhythm conditions.

  - having a family history of sudden death in individuals less than 50 years of age.
  - having heart disease (e.g., heart attack, congestive heart failure, enlarged left ventricle of the heart, diseases affecting the electrical signals of your heart).
  - having an electrolyte imbalance (e.g., low levels of potassium, magnesium or calcium in the blood).
  - having a condition that affects the brain (e.g., brain bleed, stroke, head trauma).
  - having liver or kidney problems.
  - being known to poorly metabolize certain medicines.
  - having diabetes.
  - having poor nutrition.
  - having damage to the nerves that control automatic body functions (e.g., blood pressure, temperature control, bladder function, etc.).
- are at risk of developing blood clots. Risk factors include:
  - a family history of blood clots
  - being over the age of 65
  - smoking
  - being overweight
  - having a recent major surgery (such as hip or knee replacement)
  - not being able to move due to air travel or other reasons
  - taking oral birth control ("The Pill")
- have had long-term treatment with PERPHENAZINE tablets and/or other antipsychotic medications.
- have Parkinson's disease or dementia.
- have or have had breast cancer.
- have one of the following rare hereditary diseases:
  - Galactose intolerance
  - Lapp lactase deficiency
  - Glucose-galactose malabsorption

  Because lactose is a non-medicinal ingredient in PERPHENAZINE.
- are a child or adolescent who has:
  - symptoms of Reye's syndrome (a serious condition that causes swelling in the liver and brain) such as vomiting, lack of energy, change in mental states and seizures.
  - sudden fever.
- Exercise strenuously, or are dehydrated, or are exposed or will be exposed to extreme heat. PERPHENAZINE may interfere with your body's ability to adjust to heat. Avoid becoming overheated or dehydrated (for example with vigorous exercise or exposure to extreme heat) while taking PERPHENAZINE.
- have previously had to stop taking other medicines for psychiatric problems like PERPHENAZINE (known as phenothiazines) because they have affected your blood cells or caused jaundice (yellowing of the skin and eyes).
- are pregnant, think you might be pregnant or are planning to become pregnant. PERPHENAZINE should not be used during pregnancy unless your healthcare professional considers that the benefits to you markedly outweigh the potential risks to the fetus.
- are breast-feeding or planning to breast-feed. It is not known if PERPHENAZINE can pass into your breast milk and harm a breast-fed baby.

Other warnings you should know about:

Driving and using machines: PERPHENAZINE may affect your mental and physical abilities. This may be more likely to occur when you start your treatment. Before you drive or do tasks that require special attention, wait until you know how you respond to PERPHENAZINE. You should be cautious when driving a car or operating machinery.

Testing and check-ups: Your healthcare professional may do check-ups and tests before you start taking PERPHENAZINE and regularly during your treatment. These may include:

- blood tests to monitor:
  - your blood sugar (glucose) levels;
  - your complete blood cell count. This test measures the number and quality of the red blood cells, white blood cells and platelets.
  - the health of your liver and kidneys.
- body weight checks to monitor any changes in weight.
- eye exams to monitor your visions and the health of your eyes.

If you are taking PERPHENAZINE for a long period of time and in high doses, your healthcare professional will monitor you more closely for side effects. They may adjust your dose if needed.

Pregnancy: You should not take PERPHENAZINE while you are pregnant or if you are planning on becoming pregnant unless you have talked to your healthcare professional about it. If you took PERPHENAZINE at any time while you were pregnant or if you took it before you became pregnant, the following symptoms may happen in your newborn baby:

- shaking,
- stiffness in their muscles and/or weakness,
- sleepiness,
- agitation,
- breathing problems, or
- difficulty feeding.

Get medical help right away if your newborn has any of these symptoms.

Taking PERPHENAZINE may also affect your pregnancy tests by producing false-positive or false-negative pregnancy results. PERPHENAZINE may also give false positive phenylketonuria (PKU) test results (a blood test given to newborns one to three days after birth).

Eye problems: PERPHENAZINE can cause eye problems such as mydriasis. Mydriasis is a condition where your pupils widen in an unusual way. This can cause a build-up of fluid and pressure in your eyes. Tell your healthcare professional **right away** if you experience visions changes, eye pain, redness in or around the eye.

Tardive dyskinesia (TD): Like other antipsychotic medications, PERPHENAZINE may cause potentially irreversible muscle twitching or unusual/abnormal movement of the face or tongue or other parts of your body.

Neuroleptic malignant syndrome (NMS): NMS is potentially a life-threatening condition that has been reported with the use of antipsychotic medications. Symptoms of NMS include:

- severe muscle stiffness or inflexibility with high fever,
- rapid or irregular heartbeat,
- sweating,

- state of confusion or reduced consciousness.

Call your healthcare professional **right away** if you start to have any of these symptoms while taking PERPHENAZINE.

Hyperprolactinemia (increased levels of prolactin): PERPHENAZINE can raise your levels of a hormone called "prolactin". This is measured with a blood test. Symptoms may include:

- In men:
  - swelling in the breast,
  - difficulty in getting or maintaining an erection or other sexual dysfunction.
- In women:
  - discomfort in the breasts,
  - leaking of milk from the breasts (even if not pregnant),
  - missing your menstrual period or other problems with your cycle.

If you have high levels of prolactin and a condition called hypogonadism, you may be at an increased risk of breaking a bone due to osteoporosis. This occurs in both men and women.

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

Serious drug interactions:

Serious drug interactions with PERPHENAZINE include:

- medicines that can affect how your heart beats. These include, but are not limited to:
  - medicines used to treat an abnormal heart rhythm (e.g., quinidine, procainamide, disopyramide, amiodarone, sotalol, ibutilide).
  - other antipsychotic medications (e.g., droperidol, chlorpromazine, pimozide).
  - medicines used to treat depression (e.g., fluoxetine, venlafaxine, tricyclic/tetracyclic antidepressants, selective serotonin reuptake inhibitors [SSRIs] such as citalopram).
  - opioids, medicines used to relieve pain (e.g., methadone, codeine and tramadol).
  - medicines used to treat bacterial infections (e.g., erythromycin, clarithromycin, moxifloxacin).
  - pentamidine, used to treat a serious type of pneumonia (i.e., *Pneumocystic carinii* pneumonia).
  - medicines used to treat malaria (e.g., quinine).
  - medicines used to treat fungal infections (e.g., ketoconazole, fluconazole, itraconazole, voriconazole).
  - domperidone, used to speed up the movements of the stomach and bowel.
  - tacrolimus, used to prevent organ transplant rejection.
  - other medicines used to treat nausea and vomiting (e.g., ondansetron).
  - medicines used to treat breathing problems like asthma and lung disease (e.g., salmeterol, formoterol).
  - lithium, used to treat mood disorders.
  - medicines that can cause an electrolyte imbalance (e.g., diuretics, also known as "water pills").
- medicines known as dopaminergics such as:
  - cabergoline and quinagolide, used to treat high levels of prolactin in the blood.

The following may also interact with PERPHENAZINE:

- alcohol. PERPHENAZINE can increase the effects of alcohol. You should not drink alcohol while taking PERPHENAZINE.
- anesthetics, medicines used during surgery.
- analgesics, medicines used to relieve pain.
- barbiturates, medicines used to relax the body and help with sleeping.
- medicines used to control seizures (e.g., phenytoin).
- antihistamines, medicines used to treat allergies and may cause drowsiness (e.g., diphenhydramine).
- muscle relaxants, medicines used to treat muscle spasms and back pain (e.g., dantrolene).
- sedatives and tranquilizers, medicines used to treat anxiety and/or insomnia.cisapride, used to treat gastric reflux (the regurgitation of stomach acid into the esophagus).
- medicines that may make you sleepy or drowsy (e.g., cough-and-cold medicines and sleeping pills). You should not take PERPHENAZINE if you have drowsiness caused by other medicines.
- atropine, used to treat eye problems, a low heart rate, insecticide or mushroom poisoning, or reduce saliva and fluid in the respiratory tract during surgery.
- phosphorus insecticides used for farming, treating animals (e.g., flea and tick control), and treating pests around the house or garden. PERPHENAZINE can increase the toxicity from these types of insecticides, so caution must be taken when using these products.
- medicines used treat high blood pressure and certain heart conditions (e.g., propranolol, guanethidine, guanadrel).
- oral anticoagulants, medicines used to prevent and treat blood clots (e.g., warfarin).
- antacids, used to treat indigestion.
- epinephrine, used for the emergency treatment of severe allergic reactions.
- medicines used to treat gastrointestinal problems, such as magnesium, aluminum and calcium salts, oxides and hydroxides.
- hormonal birth control.
- betel nut (also known as areca nut).

How to take PERPHENAZINE:

- Take PERPHENAZINE exactly as your healthcare professional has told you.
- Your healthcare professional will decide on the best dose for you depending on:
  - the severity of your symptoms; and
  - how you respond to your treatment.
- Your healthcare professional will give you the lowest effective dose to minimize side effects.
- Do not take PERPHENAZINE more often or increase your dose without consulting your healthcare professional. Taking more than you should will not improve your condition any faster. Instead, you will increase your risk of serious side effects.
- Do not stop taking this medicine suddenly without your healthcare professional's approval.

Usual dose:

Please note, the lower range of the adult dosages listed below may be used in children over 12 years of age.

To treat psychotic disorders:

- **Moderately disturbed, non-hospitalized patients:**

  Adult dosage range: 4 mg to 8 mg, three times a day. Maximum dose: 24 mg per day. Your healthcare professional will reduce your dose as early as possible.

- **Hospitalized patients:**
  Adult dosage range: 8 mg to 16 mg, two to four times a day. Maximum dose: 64 mg per day.

To control nausea and vomiting:

Adult dosage range: 8 mg to 16 mg daily in divided doses. 24 mg may sometimes be necessary. Your healthcare professional will reduce your dose as early as possible.

Overdose:

Symptoms of an overdose with PERPHENAZINE may include:

- involuntary movements that you cannot control,
- shaking (tremors),
- agitation,
- confusion,
- drowsiness,
- usually weak breathing,
- muscle stiffness or twitching,
- feeling restless,
- seizures,
- fever,
- low blood pressure,
- dry mouth,
- lack of normal muscle contractions in the intestines, and
- fainting.

If you think you, or a person you are caring for, have taken too much PERPHENAZINE, contact a healthcare professional, hospital emergency department, 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 possible. However, if it is almost time for your next dose, skip the missed dose and take your next dose as scheduled. Never take two doses at once to make up for a missed dose.

Possible side effects from using PERPHENAZINE:

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

Side effects with PERPHENAZINE may include:

- sweating,
- frequent urination or lack of bladder control,
- dizziness,
- drowsiness,
- dry mouth,
- stuffy nose
- nausea or vomiting,
- headache,
- menstrual cycle changes,
- changes in libido,
- swelling of the breasts and milk production in both men and women,
- changes in bodyweight,
- changes in appetite,
- increased thirst,
- skin colouring (pigmentation), skin rashes, itching or redness, flaky skin, eczema, skin sensitivity to light,
- increased salivation,
- constipation,
- fever,
- lack of energy,
- swelling in the hands, arms, legs or feet,
- fainting,
- trouble falling asleep and/or staying asleep,
- asthma.

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Unknown			
Allergic reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing, fever, asthma, wheezing, feeling sick to your stomach, itchiness, or vomiting.			✓
Behavioural changes (including worsening of psychotic symptoms): hallucinations, delusions, changes in sleep patterns, confusion,			✓

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
depression, anxiety, anger, restlessness, problems concentrating, disorientation, or agitation.			
Blood clots: swelling, pain, redness in an arm or leg that can be warm to touch, sudden chest pain, difficulty breathing, and heart palpitations, shortness of breath, chest pain while breathing, coughing up blood.		✓	
Blood disorders (low blood platelet, low white blood cell, and/or low red blood cell counts): frequent infection with fever, chills, soreness of the mouth, gums or throat, fatigue, aches, pains, flu-like symptoms, paleness of the skin, rapid heart rate, shortness of breath, bruising easily, or heavy bleeding.			✓
Exfoliative dermatitis (severe inflammation of the skin): red and peeling skin, scaling, crusting lesions, thickened skin, itching, swollen lymph nodes, fever, malaise, secondary infections (viral or bacterial)			✓
Extrapyramidal reactions: muscle stiffness, body spasms, upward eye rolling, exaggeration of reflexes, drooling, difficulty moving how and when you want, masklike face (appears to lack emotion), tremors, drooling, or dragging feet as you walk, difficultly swallowing, a feeling of restlessness, or inability to remain motionless.			✓
Eye problems: increased pressure in the eye, sensitivity to light, eye pain, headache, vision changes (such as blurred vision, halos around lights, glare, distorted vision, dark or blind spots in the		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
center of your vision, or difficulty with depth perception), swelling or redness in or around the eye			
Heart problems: abnormally fast heartbeat, irregular heartbeat, chest pain, or changes in the rhythm of your heart.			✓
Hyperglycemia (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision and fatigue.	✓		
Hyperprolactinemia (increased levels of prolactin): In men: swelling in the breast, difficulty in getting or maintaining an erection, or other sexual dysfunction. In women: discomfort in the breasts, leaking of milk from the breasts (even if not pregnant), or missing your menstrual period or other problems with your cycle.		✓	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, or fatigue (may occur when you go from lying or sitting to standing up).		✓	
Liver problems (including biliary stasis, cholestatic jaundice): upper right abdominal pain, pain in the back, nausea, vomiting, yellowing of the skin and white of eyes, dark urine, light coloured stool, or itching all over your body.			✓
Lupus erythematosus-like syndrome: pain and swelling in the joints, skin rash, fatigue, fever.		✓	
Neuroleptic malignant syndrome (NMS): pronounced muscle stiffness or inflexibility with high fever, rapid or irregular heartbeat, sweating, state of confusion, or reduced consciousness.			✓

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Overheating/dehydration (dry mouth, excessive thirst): thirst, headache, loss of appetite, feel tired and weak, lack of sweating, decreased blood pressure and urine, dark yellow urine.	✓		
Paralytic ileus (muscles that move food through the intestines are paralyzed): new or worsening constipation, nausea, vomiting, dehydration, gas, or abdominal pain		✓	
Priapism (persistent and painful erection of the penis lasting longer than 4 hours).			✓
Seizures (fits): loss of consciousness with uncontrollable shaking.			✓
Tardive dyskinesia (TD): uncontrollable, unusual, or abnormal movements, muscle twitches of the body, face, mouth, eyes or tongue, or stretching the neck and body.		✓	

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

Reporting side effects

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

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) 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 controlled room temperature (between 15°C to 30°C).
- Do not use after the expiry date shown on the bottle.
- Keep out of reach and sight of children.

If you want more information about PERPHENAZINE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (http://www.aapharma.ca/en/); or by calling 1-877-998-9097.

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