PRESCRIBING INFORMATION

PERPHENAZINE

Perphenazine Tablets USP

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

Antipsychotic/Antiemetic

AA Pharma Inc.
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2 mg, 4 mg, 8 mg and 16 mg

THERAPEUTIC CLASSIFICATION

Antipsychotic/Antiemetic

ACTIONS AND CLINICAL PHARMACOLOGY

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

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.

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. Perphenazine distributes to most body tissues with high concentrations being distributed into liver and spleen. Perphenazine enters the enterohepatic circulation and is excreted chiefly in the feces.

INDICATIONS AND CLINICAL USE

Perphenazine is indicated in the management of manifestations of psychotic disorders.

It is also effective in 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 mental retardation.

CONTRAINDICATIONS

Should not be administered in the presence of circulatory collapse, altered states of consciousness or comatose states, particularly when these are due to intoxication with central depressant drugs (alcohol, hypnotics, narcotics). It is contraindicated in severely depressed patients, in the presence of blood dyscrasias, liver disease, renal insufficiency, pheochromocytoma, or in patients with severe cardiovascular disorders or a history of hypersensitivity to phenothiazine derivatives.

As with other phenothiazines, Perphenazine is contraindicated in patients with suspected or established subcortical brain damage, with or without hypothalamic damage, since a hyperthermic reaction with temperatures above 40^{o}C may occur, sometimes not until 14 to 16 hours after drug administration.

Phenothiazine compounds should not be used in patients receiving large doses of hypnotics, due to the possibility of potentiation.

Perphenazine is contraindicated in children undergoing surgery.

WARNINGS

The antiemetic action of Perphenazine 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 or intestinal obstruction. Therefore the etiology of nausea and vomiting should be established before using the drug.

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.

Elderly Patients with Dementia

Analyses of thirteen placebo controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in elderly patients with dementia showed a mean 1.6 fold increase in the death rate in the drug treated patients. 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. PERPHENAZINE is not indicated in dementia-related psychosis (see PRECAUTIONS, Use in the Elderly).

Occupational Hazards

The use of this drug 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.

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. Older patients are at increased risk for development of tardive dyskinesia. 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 treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. 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. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, especially in the elderly, 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.

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, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

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.

Special Populations: Pregnant Women

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.

Non-Teratogenic Effects: Neonates exposed to antipsychotic drugs (including Perphenazine) 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.

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

Children

Perphenazine is not recommended for children less than 12 years of age.

The extrapyramidal symptoms which can occur secondary to Perphenazine 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 should be avoided in children and adolescents whose signs and symptoms suggest Reye's syndrome.

PRECAUTIONS

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.

Phenothiazines may increase the effects of general anesthetics, opiates, barbiturates, and other CNS depressants and the doses of these drugs should be reduced if administered concomitantly with Perphenazine.

On long-term therapy, particularly during the first 2 or 3 months, it is advisable to perform periodic liver function tests and blood counts as cholestatic jaundice and blood dyscrasias may occur, necessitating discontinuation of treatment. Renal function should be monitored and, if BUN becomes abnormal, treatment should be discontinued.

To lessen the likelihood of adverse reactions related to drug accumulation, patients on long-term therapy, particularly on high doses, should be evaluated periodically to decide whether the maintenance dosage could be lowered or drug therapy discontinued.

Because of its anticholinergic action, Perphenazine should be used with great caution in patients with glaucoma or prostatic hypertrophy.

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

Retinal changes, lenticular and corneal deposits and abnormal skin pigmentation have been observed with other phenothiazines and may occur after prolonged therapy. The possibility of persistent tardive dyskinesia should also be borne in mind when patients are under long-term treatment.

Patients receiving Perphenazine should be cautioned against exposure to extreme heat or organophosphorous insecticides.

Hypotension and ECG changes, particularly non-specific and usually reversible Q and T wave distortions, have been associated with the administration of phenothiazines. 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. As well, concomitant treatment with other drugs known to cause QT prolongation should be avoided in combination with perphenazine. Medications that prolong the QT interval include dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, some other antipsychotics (e.g., mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide), sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol or tacrolimusTherefore, Perphenazine should be used with caution in patients with compensated cardiovascular and cerebrovascular disorders.

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible rick factors for

VTE should be identified before and during treatment with perphenazine and preventive measures undertaken.

Unexpected, sudden deaths have occurred in hospitalized patients treated with phenothiazines. Previous brain damage or seizures may predispose. High doses should be avoided in known seizure patients. Sudden exacerbations of psychotic behaviour patterns occurred in several patients shortly before death. Acute fulminating pneumonia or pneumonitis and aspiration of gastric contents were also observed. Therefore, the physician also should keep in mind the possible development of silent pneumonias.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies, nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

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

Genitourinary: Rare cases of priapism have been reported with antipsychotic use, such as Perphenazine. This adverse reaction, as with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment.

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.

Older Patients

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.

Children

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.

ADVERSE EFFECTS

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 doctor if constipation occurs or worsens, as they may need laxatives.

Hematologic

Observational studies and/or case reports of venous thromboembolism (VTE), including fatal pulmonary embolism, have been reported with antipsychotic drugs, including Perphenazine. When prescribing Perphenazine, all potential risk factors for VTE should be identified and preventive measures undertaken.

Neurological

Extrapyramidal reactions including tremor, rigidity, akathisia, dystonia, dyskinesia, oculogyric crises, opisthotonos, hyperreflexia and sialorrhea. EEG changes, disturbed temperature regulation and seizures have also been encountered.

Persistent Tardive Dyskinesia

As with other antipsychotic agents, tardive dyskinesia may occur in patients on long-term therapy or may be observed after drug therapy has been discontinued. The risk seems to be greater in elderly patients on high doses, especially females. The symptoms are persistent and in some patients appear to be irreversible. 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.

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. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked. 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. 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.

Behavioral

Sleep disturbances, drowsiness, fatigue, 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.

Autonomic Nervous System

Dry mouth, nasal congestion, headache, nausea, constipation, tachycardia, hypotension, syncope, dizziness, blurred vision, vomiting, sweating and urinary incontinence have been observed.

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. 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.

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

Metabolic and Endocrine

Anorexia, menstrual irregularities, impotence, and increased thirst, weight changes, increased appetite, peripheral edema, galactorrhea, gynecomastia, false positive pregnancy tests, and changes in libido have also occurred in patients receiving phenothiazine therapy.

Allergic or Toxic

Pruritus, dermatitis, rash, erythema, urticaria, seborrhea, eczema, exfoliative dermatitis, and photosensitivity. The possibility of an anaphylactoid reaction should be borne in mind.

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.

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

Miscellaneous

The following adverse reactions have been reported in patients receiving phenothiazine derivatives: headache, asthma, laryngeal, cerebral and angioneurotic edema, altered cerebrospinal fluid proteins,

systemic lupus erythematosus-like syndrome, hyperpyrexia, ECG and EEG changes and hypotension severe enough to cause fatal cardiac arrest. Skin pigmentation, epithelial keratopathy, lenticular and corneal deposits have been associated with long-term administration.

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.

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

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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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's antiemetic action. Limited experience indicates that phenothiazines are not dialyzable.

DOSAGE AND ADMINISTRATION

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 to 16 mg may be given in divided amounts. The lower range of adult dosage may be used in children over 12.

To treat psychotic disorders:

Moderately disturbed nonhospitalized 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.

STORAGE AND STABILITY

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

AVAILABILITY OF DOSAGE FORMS

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

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

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

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

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

PERPHENAZINE

Perphenazine Tablets USP

This leaflet is part III of a three-part "Product Monograph" published when PERPHENAZINE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PERPHENAZINE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Perphenazine is used to:

- To treat psychotic disorders
- To control nausea and vomiting

What it does:
PERPHENAZINE is an antipsychotic medication which affects chemicals in the brain that allow communications between nerve cells (neurotransmitters). These chemicals are called dopamine and serotonin. Exactly how PERPHENAZINE works is unknown. However, it seems to readjust the balance of dopamine and serotonin.

When it should not be used:

You should not use PERPHENAZINE if you have:

- An allergy to Perphenazine, to any of its ingredients or to phenothiazines
- A medical condition known as pheochromocytoma (a tumor of the adrenal gland)
- A severe heart or blood vessel disorder
- Severe kidney problems
- Had brain damage
- Liver disease
- A blood cell disorder such as anemia, low white blood cell counts, or low platelets
- Drowsiness, slow breathing, weak pulse

- Decreased alertness caused by taking certain medications or drinking alcohol

- You are going to receive anesthesia in the spine or for a region (such as an arm, leg or the lower part of your body)

What the medicinal ingredient is:
Perphenazine

What the nonmedicinal ingredients are:
Carnauba wax, croscarmellose sodium, dextrates and magnesium stearate; film coat: D&C Yellow No. 10 Lake, FD&C Yellow No. 6 Lake, hydroxypropyl methylcellulose, polyethylene glycol and titanium dioxide.

What dosage forms it comes in:
Tablets: 2, 4, 8 and 16 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Studies with various medicines of the group to which PERPHENAZINE belongs, when used in the elderly patients with dementia, have been associated with an increased rate of death. PERPHENAZINE is not indicated in elderly patients with dementia.

Before you use PERPHENAZINE talk to your doctor or pharmacist if:

- You have heart disease, glaucoma or prostatic hypertrophy

- You are addicted to alcohol. You should not take PERPHENAZINE if you are under the effects of alcohol.

- You are pregnant. PERPHENAZINE should not be used during pregnancy unless your doctor considers the benefits to you markedly outweighs the potential risks to the fetus

- You are taking barbiturates, painkillers, narcotics or, antihistamines or other drugs that make you drowsy.

- You have any allergies to this drug or its ingredients

- You have or ever had a blackout or seizure

- You are breastfeeding.

- You are breastfeeding.

IMPORTANT: PLEASE READ

PERPHENAZINE may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. You should be cautious when performing potentially hazardous tasks.

Effects on Newborns:
In some cases, babies born to a mother taking PERPHENAZINE 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 are having difficulty feeding.

People who take PERPHENAZINE are cautioned:

- Against exposure to extreme heat
- That drugs such as PERPHENAZINE increase the toxicity of certain types of insecticides ("organophosphorous" insecticides) including insecticides for agriculture (farming), treating animals (flea and tick control) and for treating pests around the house and garden. Be cautious if you must use these products while taking PERPHENAZINE

INTERACTIONS WITH THIS MEDICATION

PERPHENAZINE can add to the effects of alcohol. You should avoid consuming alcoholic beverages while on PERPHENAZINE therapy.

Tell your doctor about all your prescription and over-the-counter medications, vitamins, minerals, herbal products (such as St. John's Wort), and drugs prescribed by other doctors. Do not start a new medication without telling your doctor.

Before using PERPHENAZINE, tell your doctor if you regularly use other medicines that make you sleepy (such as cold or allergy medicine, narcotic pain medicine, sleeping pills, muscle relaxants, and medicine for seizures, depression, or anxiety). You should not take PERPHENAZINE if you have drowsiness caused by other medications.

Drugs that may interact with PERPHENAZINE include: anti-anxiety agents, antidepressants, muscle relaxants, anti-seizure medicine, high blood pressure medicine, cabergoline, metrizamide, guanethidine, guanadrel, grepafloxacin, sparfloxacin, lithium, cisapride, atropine-like drugs, narcotic pain relievers (e.g., codeine), drugs used to aid sleep, drowsiness-causing antihistamines (e.g., diphenhydramine), other drugs that may make you drowsy.

Many cough-and-cold products contain ingredients that may add a drowsiness effect. Before using cough-and-cold medications, ask your doctor or pharmacist about the safe use of those products. Do not start or stop any medicine without doctor or pharmacist approval.

This list is not complete and there may be other drugs that can interact with PERPHENAZINE.

IMPORTANT: PLEASE READ

PROPER USE OF THIS MEDICATION

Take this medication by mouth exactly as prescribed. During the first few days your doctor may gradually increase your dose to allow your body to adjust to the medication. Do not take this more often or increase your dose without consulting your doctor. 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 doctor's approval.

Your doctor will decide which dose is best for you.

Usual dose:

Your doctor should adjust your dose according to the severity of your condition and the response obtained. Unless you are hospitalized, your dose ordinarily 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 use the lowest effective dose since extrapyramidal symptoms increase in frequency and severity with increased dosage. If you are taking PERPHENAZINE to control severe nausea and vomiting, you may be prescribed daily doses of 8 to 16 mg given in divided amounts. The lower range of adult dosage may be used in children over 12.

To treat psychotic disorders:

Moderately disturbed nonhospitalized patients with schizophrenia

4 to 8 mg three times a day initially; reduce as soon as possible to the lowest effective dose.

Hospitalized patients with schizophrenia
8 to 16 mg two to four times a day; the dose should not exceed 64 mg a day.

To control nausea and vomiting:

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

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Overdose symptoms may include agitation, and confusion, drowsiness, dizziness, muscle stiffness or twitching, increased salivation, trouble swallowing, weakness, loss of balance or coordination, and fainting.

IMPORTANT: PLEASE READ

Missed Dose:

Take the missed dose as soon as you remember. If it is almost time for your next dose, wait until then to take the medicine and skip the missed dose. Do not double your dose to make up the missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like other medications, PERPHENAZINE may cause some side effects. These side effects may be minor and temporary. However, some may be serious and need medical attention.

Side effects may include: sweating, urinary incontinence, dizziness, drowsiness, dry mouth, nasal congestion, nausea and vomiting, headache, menstrual changes, change in libido, swelling of the breasts and milk production in both men and women, weight changes and blurred vision.
If any of these affects you severely, tell your doctor.

Your doctor should check your body weight before starting PERPHENAZINE and continue to monitor it for as long as you are being treated.

Your doctor should take blood tests before starting PERPHENAZINE. They will monitor blood sugar, and the number of infection fighting white blood cells. Your doctor should continue to monitor your blood for as long as you are being treated.

IMPORTANT: PLEASE READ

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.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Unknown	**Allergic Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
	Neuroleptic Malignant Syndrome: any group of symptoms which may include high fever, sweating, stiff muscles, fast heartbeat, fast breathing and feeling confused, drowsy or agitated			✓
	Extrapyramidal Symptoms: muscle stiffness, body spasm, upward eye rolling, exaggeration of reflexes, drooling, difficulty moving how and when you want.			✓

IMPORTANT: PLEASE READ

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
	Fast or irregular heartbeat		✓	
	Seizures or fits			✓
	Long-lasting (greater than 4 hours in duration) and painful erection of the penis			✓
	Tardive Dyskinesia: uncontrollable movements or twitches of the body, face, eyes or tongue, stretching the neck and body		✓	
	Low Blood Pressure: feeling of Lightheaded-ness or fainting especially when getting up from a lying or sitting position)		✓	
	High Blood Pressure: headaches, vision disorders, nausea and vomiting		✓	
	Decreased sweating		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your**
	Jaundice: yellow colour to skin and eyes, dark urine		✓	
	Respiratory Infection: fever, flu-like symptoms, coughing, difficult or fast breathing		✓	
	New or worsening constipation		✓	
	Blood Clots: swelling, pain and redness in an arm or leg that is warm to touch. You may develop sudden chest pain, difficulty breathing and heart palpitations		✓	
	Akathisia: a feeling of restlessness, inability to remain motionless		✓	
	Vision Changes: blurred vision, glaucoma or other eye disorder		✓	
	Increased Blood Sugar: frequent urination, thirst and hunger		✓	

This is not a complete list of side effects. For any unexpected effects while taking PERPHENAZINE, contact your doctor or pharmacist.

IMPORTANT: PLEASE READ

HOW TO STORE IT

Store at controlled room temperature (between 15 to 30°C). Do not use after the expiry date shown on the bottle.

Keep this and all medications out of the reach and sight of children.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.aapharma.ca
or by contacting the sponsor, AA Pharma Inc. at:
(905)669-0528 or 1-800-667-4708

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REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect/index-eng.php
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Omtario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.