Attachment I

2004 Phenergan® Labeling

Wyeth®

Phenergan®

(promethazine HCl)
Tablets and Suppositories

only

DESCRIPTION

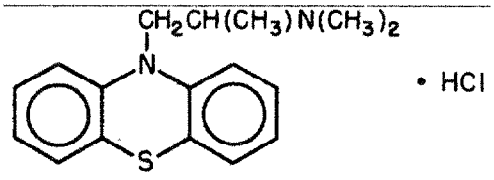
Each tablet of Phenergan contains 12.5 mg, 25 mg, or 50 mg promethazine HCl. The inactive ingredients present are lactose, magnesium stearate, and methylcellulose. Each dosage strength also contains the following:

12.5 mg–FD&C Yellow 6 and saccharin sodium;
25 mg–saccharin sodium;
50 mg–FD&C Red 40.

Each rectal suppository of Phenergan contains 12.5 mg, 25 mg, or 50 mg promethazine HCl with ascorbyl palmitate, silicon dioxide, white wax, and cocoa butter. Phenergan Suppositories are for rectal administration only.

Promethazine HCl is a racemic compound; the empirical formula is $C_{17}H_{20}N_2S{\bullet}HCl$ and its molecular weight is 320.88.

Promethazine HCl, a phenothiazine derivative, is designated chemically as 10*H*-Phenothiazine-10-ethanamine, *N,N,*α-trimethyl-, monohydrochloride, (±)- with the following structural formula:



Promethazine HCl occurs as a white to faint yellow, practically odorless, crystalline powder which slowly oxidizes and turns blue on prolonged exposure to air. It is freely soluble in water and soluble in alcohol.

CLINICAL PHARMACOLOGY

Promethazine is a phenothiazine derivative which differs structurally from the antipsychotic phenothiazines by the presence of a branched side chain and no ring substitution. It is thought that this configuration is responsible for its relative lack (1/10 that of chlorpromazine) of dopamine antagonist properties.

Promethazine is an H_1 receptor blocking agent. In addition to its antihistaminic action, it provides clinically useful sedative and antiemetic effects.

Promethazine is well absorbed from the gastrointestinal tract. Clinical effects are apparent within 20 minutes after oral administration and generally last four to six hours, although they may persist as long as 12 hours. Promethazine is metabolized by the liver to a variety of compounds; the sulfoxides of promethazine and N-demethylpromethazine are the predominant metabolites appearing in the urine.

INDICATIONS AND USAGE

Phenergan, either orally or by suppository, is useful for:

Perennial and seasonal allergic rhinitis.

Vasomotor rhinitis.

Allergic conjunctivitis due to inhalant allergens and foods.

Mild, uncomplicated allergic skin manifestations of urticaria and angioedema.

Amelioration of allergic reactions to blood or plasma.

Dermographism.

Anaphylactic reactions, as adjunctive therapy to epinephrine and other standard measures, after the acute manifestations have been controlled.

Preoperative, postoperative, or obstetric sedation.

Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.

Therapy adjunctive to meperidine or other analgesics for control of post-operative pain.

Sedation in both children and adults, as well as relief of apprehension and production of light sleep from which the patient can be easily aroused.

Active and prophylactic treatment of motion sickness.

Antiemetic therapy in postoperative patients.

CONTRAINDICATIONS

Phenergan Tablets and Suppositories are contraindicated for use in pediatric patients less than two years of age.

Phenergan Tablets and Suppositories are contraindicated in comatose states, and in individuals known to be hypersensitive or to have had an idiosyncratic reaction to promethazine or to other phenothiazines.

Antihistamines are contraindicated for use in the treatment of lower respiratory tract symptoms including asthma.

WARNINGS

PHENERGAN SHOULD NOT BE USED IN PEDIATRIC PATIENTS LESS THAN 2 YEARS OF AGE BECAUSE OF THE POTENTIAL FOR FATAL RESPIRATORY DEPRESSION.

POSTMARKETING CASES OF RESPIRATORY DEPRESSION, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH USE OF PHENERGAN IN PEDIATRIC PATIENTS LESS THAN 2 YEARS OF AGE. A WIDE RANGE OF WEIGHT-BASED DOSES OF PHENERGAN HAVE RESULTED IN RESPIRATORY DEPRESSION IN THESE PATIENTS.

CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PHENERGAN TO PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER. IT IS RECOMMENDED THAT THE LOWEST EFFECTIVE DOSE OF PHENERGAN BE USED IN PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER AND CONCOMITANT ADMINISTRATION OF OTHER DRUGS WITH RESPIRATORY DEPRESSANT EFFECTS BE AVOIDED.

CNS Depression

Phenergan Tablets and Suppositories may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The impairment may be amplified by concomitant use of other central-nervous-system depressants such as alcohol, sedatives/hypnotics (including barbiturates), narcotics, narcotic analgesics, general anesthetics, tricyclic antidepressants, and tranquilizers; therefore such agents should either be eliminated or given in reduced dosage in the presence of promethazine HCl (see **PRECAUTIONS–Information for Patients** and **Drug Interactions**).

Respiratory Depression

Phenergan Tablets and Suppositories may lead to potentially fatal respiratory depression.

Use of Phenergan Tablets and Suppositories in patients with compromised respiratory function (e.g., COPD, sleep apnea) should be avoided.

Lower Seizure Threshold

Phenergan Tablets and Suppositories may lower seizure threshold. It should be used with caution in persons with seizure disorders or in persons who are using concomitant medications, such as narcotics or local anesthetics, which may also affect seizure threshold.

Bone-Marrow Depression

Phenergan Tablets and Suppositories should be used with caution in patients with bone-marrow depression. Leukopenia and agranulocytosis have been reported, usually when Phenergan (promethazine HCl) has been used in association with other known marrow-toxic agents.

Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with promethazine HCl alone or in combination 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 promethazine HCl, antipsychotic drugs, if any, 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.

Since recurrences of NMS have been reported with phenothiazines, the reintroduction of promethazine HCl should be carefully considered.

Use in Pediatric Patients

PHENERGAN TABLETS AND SUPPOSITORIES ARE CONTRAINDICATED FOR USE IN PEDIATRIC PATIENTS LESS THAN TWO YEARS OF AGE.

CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PHENERGAN TABLETS AND SUPPOSITORIES TO PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER BECAUSE OF THE POTENTIAL FOR FATAL RESPIRATORY DEPRESSION. RESPIRATORY DEPRESSION AND APNEA, SOMETIMES ASSOCIATED WITH DEATH, ARE STRONGLY ASSOCIATED WITH PROMETHAZINE PRODUCTS AND ARE NOT DIRECTLY RELATED TO INDIVIDUALIZED WEIGHT-BASED DOSING, WHICH MIGHT OTHERWISE PERMIT SAFE ADMINISTRATION. CONCOMITANT ADMINISTRATION OF PROMETHAZINE PRODUCTS WITH OTHER RESPIRATORY DEPRESSANTS HAS AN ASSOCIATION WITH RESPIRATORY DEPRESSION, AND SOMETIMES DEATH, IN PEDIATRIC PATIENTS.

ANTIEMETICS ARE NOT RECOMMENDED FOR TREATMENT OF UNCOMPLICATED VOMITING IN PEDIATRIC PATIENTS, AND THEIR USE SHOULD BE LIMITED TO PROLONGED VOMITING OF KNOWN ETIOLOGY. THE EXTRAPYRAMIDAL SYMPTOMS WHICH CAN OCCUR SECONDARY TO PHENERGAN TABLETS AND SUPPOSITORIES ADMINISTRATION MAY BE CONFUSED WITH THE CNS SIGNS OF UNDIAGNOSED PRIMARY DISEASE, e.g., ENCEPHALOPATHY OR REYE'S SYNDROME. THE USE OF PHENERGAN TABLETS AND SUPPOSITORIES SHOULD BE AVOIDED IN PEDIATRIC PATIENTS WHOSE SIGNS AND SYMPTOMS MAY SUGGEST REYE'S SYNDROME OR OTHER HEPATIC DISEASES.

Excessively large dosages of antihistamines, including Phenergan Tablets and Suppositories, in pediatric patients may cause sudden death (see **OVERDOSAGE**). Hallucinations and convulsions have occurred with therapeutic doses and overdoses of Phenergan in pediatric patients. In pediatric patients who are acutely ill associated with dehydration, there is an increased susceptibility to dystonias with the use of promethazine HCl.

Other Considerations

Administration of promethazine HCl has been associated with reported cholestatic jaundice.

PRECAUTIONS

General

Drugs having anticholinergic properties should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, and bladder-neck obstruction.

Phenergan Tablets and Suppositories should be used cautiously in persons with cardiovascular disease or with impairment of liver function.

Information for Patients

Phenergan Tablets and Suppositories may cause marked drowsiness or impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The use of alcohol or other central-nervous-system depressants such as sedatives/hypnotics (including barbiturates), narcotics, narcotic analgesics, general anesthetics, tricyclic antidepressants, and tranquilizers, may enhance impairment (see **WARNINGS–CNS Depression** and **PRECAUTIONS–Drug Interactions**). Pediatric patients should be supervised to avoid potential harm in bike riding or in other hazardous activities.

Patients should be advised to report any involuntary muscle movements.

Avoid prolonged exposure to the sun.

Drug Interactions

CNS Depressants - Phenergan Tablets and Suppositories may increase, prolong, or intensify the sedative action of other central-nervous-system depressants, such as alcohol, sedatives/hypnotics (including barbiturates), narcotics, narcotic analgesics, general anesthetics, tricyclic antidepressants, and tranquilizers; therefore, such agents should be avoided or administered in reduced dosage to patients receiving promethazine HCl. When given concomitantly with Phenergan Tablets and Suppositories, the dose of barbiturates should be reduced by at least one-half, and the dose of narcotics should be reduced by one-quarter to one-half. Dosage must be individualized. Excessive amounts of promethazine HCl relative to a narcotic may lead to restlessness and motor hyperactivity in the patient with pain; these symptoms usually disappear with adequate control of the pain.

Epinephrine - Because of the potential for Phenergan to reverse epinephrine's vasopressor effect, epinephrine should NOT be used to treat hypotension associated with Phenergan Tablets and Suppositories overdose.

Anticholinergics - Concomitant use of other agents with anticholinergic properties should be undertaken with caution.

Monoamine Oxidase Inhibitors (MAOI) - Drug interactions, including an increased incidence of extrapyramidal effects, have been reported when some MAOI and phenothiazines are used concomitantly. This possibility should be considered with Phenergan Tablets and Suppositories.

Drug/Laboratory Test Interactions

The following laboratory tests may be affected in patients who are receiving therapy with promethazine HCl:

Pregnancy Tests

Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.

Glucose Tolerance Test

An increase in blood glucose has been reported in patients receiving promethazine HCl.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to assess the carcinogenic potential of promethazine, nor are there other animal or human data concerning carcinogenicity, mutagenicity, or impairment of fertility with this drug. Promethazine was nonmutagenic in the *Salmonella* test system of Ames.

Pregnancy

Teratogenic Effects–Pregnancy Category C

Teratogenic effects have not been demonstrated in rat-feeding studies at doses of 6.25 and 12.5 mg/kg of promethazine HCl. These doses are from approximately 2.1 to 4.2 times the maximum recommended total daily dose of promethazine for a 50-kg subject, depending upon the indication for which the drug is prescribed. Daily doses of 25 mg/kg intraperitoneally have been found to produce fetal mortality in rats.

Specific studies to test the action of the drug on parturition, lactation, and development of the animal neonate were not done, but a general preliminary study in rats indicated no effect on these parameters. Although antihistamines have been found to produce fetal mortality in rodents, the pharmacological effects of histamine in the rodent do not parallel those in man. There are no adequate and well-controlled studies of Phenergan® Tablets and Suppositories in pregnant women.

Phenergan (promethazine HCl) Tablets and Suppositories should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Phenergan Tablets and Suppositories administered to a pregnant woman within two weeks of delivery may inhibit platelet aggregation in the newborn.

Labor and Delivery

Promethazine HCl may be used alone or as an adjunct to narcotic analgesics during labor (see **DOSAGE AND ADMINISTRATION**). Limited data suggest that use of Phenergan during labor and delivery does not have an appreciable effect on the duration of labor or delivery and does not increase the risk of need for intervention in the newborn. The effect on later growth and development of the newborn is unknown. (See also *Nonteratogenic Effects*.)

Nursing Mothers

It is not known whether promethazine HCl is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Phenergan Tablets and Suppositories, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

PHENERGAN TABLETS AND SUPPOSITORIES ARE CONTRAINDICATED FOR USE IN PEDIATRIC PATIENTS LESS THAN TWO YEARS OF AGE (see **WARNINGS–Black Box Warning** and **Use in Pediatric Patients**).

Phenergan Tablets and Suppositories should be used with caution in pediatric patients 2 years of age and older (see **WARNINGS–Use in Pediatric Patients**).

Geriatric Use

Clinical studies of Phenergan formulations did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of Phenergan Tablets and Suppositories and observed closely.

ADVERSE REACTIONS

Central Nervous System

Drowsiness is the most prominent CNS effect of this drug. Sedation, somnolence, blurred vision, dizziness; confusion, disorientation, and extrapyramidal symptoms such as oculogyric crisis, torticollis, and tongue protrusion; lassitude, tinnitus, incoordination, fatigue, euphoria, nervousness, diplopia, insomnia, tremors, convulsive seizures, excitation, catatonic-like states, hysteria. Hallucinations have also been reported.

Cardiovascular–Increased or decreased blood pressure, tachycardia, bradycardia, faintness.

Dermatologic–Dermatitis, photosensitivity, urticaria.

Hematologic–Leukopenia, thrombocytopenia, thrombocytopenic purpura, agranulocytosis.

Gastrointestinal–Dry mouth, nausea, vomiting, jaundice.

Respiratory–Asthma, nasal stuffiness, respiratory depression (potentially fatal) and apnea (potentially fatal). (See **WARNINGS–Respiratory Depression**.)

Other–Angioneurotic edema. Neuroleptic malignant syndrome (potentially fatal) has also been reported. (See **WARNINGS–Neuroleptic Malignant Syndrome**.)

Paradoxical Reactions

Hyperexcitability and abnormal movements have been reported in patients following a single administration of promethazine HCl. Consideration should be given to the discontinuation of promethazine HCl and to the use of other drugs if these reactions occur. Respiratory depression, nightmares, delirium, and agitated behavior have also been reported in some of these patients.

OVERDOSAGE

Signs and symptoms of overdosage with promethazine HCl range from mild depression of the central nervous system and cardiovascular system to profound hypotension, respiratory depression, unconsciousness, and sudden death. Other reported reactions include hyperreflexia, hypertonia, ataxia, athetosis, and extensor-plantar reflexes (Babinski reflex).

Stimulation may be evident, especially in children and geriatric patients. Convulsions may rarely occur. A paradoxical-type reaction has been reported in children receiving single doses of 75 mg to 125 mg orally, characterized by hyperexcitability and nightmares.

Atropine-like signs and symptoms–dry mouth, fixed, dilated pupils, flushing, as well as gastrointestinal symptoms–may occur.

Treatment

Treatment of overdosage is essentially symptomatic and supportive. Only in cases of extreme overdosage or individual sensitivity do vital signs, including respiration, pulse, blood pressure, temperature, and EKG, need to be monitored. Activated charcoal orally or by lavage may be given, or sodium or magnesium sulfate orally as a cathartic. Attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Diazepam may be used to control convulsions. Acidosis and electrolyte losses should be corrected. Note that any depressant effects of promethazine HCl are not reversed by naloxone. Avoid analeptics which may cause convulsions.

The treatment of choice for resulting hypotension is administration of intravenous fluids, accompanied by repositioning if indicated. In the event that vasopressors are considered for the management of severe hypotension which does not respond to intravenous fluids and repositioning, the administration of norepinephrine or phenylephrine should be considered. EPINEPHRINE SHOULD NOT BE USED, since its use in patients with partial adrenergic blockade may further lower the blood pressure. Extrapyramidal reactions may be treated with anticholinergic antiparkinsonian agents, diphenhydramine, or barbiturates. Oxygen may also be administered.

Limited experience with dialysis indicates that it is not helpful.

DOSAGE AND ADMINISTRATION

Phenergan Tablets and Phenergan Rectal Suppositories are contraindicated for children under 2 years of age (see **WARNINGS–Black Box Warning** and **Use in Pediatric Patients**).

Phenergan Suppositories are for rectal administration only.

Allergy

The average oral dose is 25 mg taken before retiring; however, 12.5 mg may be taken before meals and on retiring, if necessary. Single 25-mg doses at bedtime or 6.25 to 12.5 mg taken three times daily will usually suffice. After initiation of treatment in children or adults, dosage should be adjusted to the smallest amount adequate to relieve symptoms. The administration of promethazine HCl in 25-mg doses will control minor transfusion reactions of an allergic nature.

Motion Sickness

The average adult dose is 25 mg taken twice daily. The initial dose should be taken one-half to one hour before anticipated travel and be repeated 8 to 12 hours later, if necessary. On succeeding days of travel, it is recommended that 25 mg be given on arising and again before the evening meal. For children, Phenergan Tablets, Syrup, or Rectal Suppositories, 12.5 to 25 mg, twice daily, may be administered.

Nausea and Vomiting

Antiemetics should not be used in vomiting of unknown etiology in children and adolescents (see **WARNINGS-Use in Pediatric Patients**).

The average effective dose of Phenergan for the active therapy of nausea and vomiting in children or adults is 25 mg. When oral medication cannot be tolerated, the dose should be given parenterally (cf. Phenergan Injection) or by rectal suppository. 12.5- to 25-mg doses may be repeated, as necessary, at 4- to 6-hour intervals.

For nausea and vomiting in children, the usual dose is 0.5 mg per pound of body weight, and the dose should be adjusted to the age and weight of the patient and the severity of the condition being treated.

For prophylaxis of nausea and vomiting, as during surgery and the postoperative period, the average dose is 25 mg repeated at 4- to 6-hour intervals, as necessary.

Sedation

This product relieves apprehension and induces a quiet sleep from which the patient can be easily aroused. Administration of 12.5 to 25 mg Phenergan by the oral route or by rectal suppository at bedtime will provide sedation in children. Adults usually require 25 to 50 mg for nighttime, presurgical, or obstetrical sedation.

Pre- and Postoperative Use

Phenergan in 12.5- to 25-mg doses for children and 50-mg doses for adults the night before surgery relieves apprehension and produces a quiet sleep.

For preoperative medication, children require doses of 0.5 mg per pound of body weight in combination with an appropriately reduced dose of narcotic or barbiturate and the appropriate dose of an atropine-like drug. Usual adult dosage is 50 mg Phenergan with an appropriately reduced dose of narcotic or barbiturate and the required amount of a belladonna alkaloid.

Postoperative sedation and adjunctive use with analgesics may be obtained by the administration of 12.5 to 25 mg in children and 25- to 50-mg doses in adults.

Phenergan Tablets and Phenergan Rectal Suppositories are contraindicated for children under 2 years of age.

HOW SUPPLIED

Phenergan® (promethazine HCl) Tablets are available as follows:

12.5 mg, orange tablet with "WYETH" on one side and "19" on the scored reverse side.

NDC 0008-0019-01, bottle of 100 tablets.

25 mg, white tablet with "WYETH" and "27" on one side and scored on the reverse side.

NDC 0008-0027-02, bottle of 100 tablets.

NDC 0008-0027-07, Redipak® carton of 100 tablets (10 blister strips of 10).

50 mg, pink tablet with "WYETH" on one side and "227" on the other side.

NDC 0008-0227-01, bottle of 100 tablets.

Keep tightly closed.

Store at controlled room temperature 20° to 25°C (68° to 77°F).

Protect from light.

Dispense in light-resistant, tight container.

Use carton to protect contents from light.

Phenergan® (promethazine HCl) Rectal Suppositories are available in boxes of 12 as follows:

12.5 mg, ivory, torpedo-shaped suppository wrapped in copper-colored foil, NDC 0008-0498-01.

25 mg, ivory, torpedo-shaped suppository wrapped in light-green foil, NDC 0008-0212-01.

50 mg, ivory, torpedo-shaped suppository wrapped in blue foil, NDC 0008-0229-01.

Store refrigerated between 2°-8°C (36°-46°F).

Dispense in well-closed container.

Wyeth®

Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

(b) (4)