DESCRIPTION
Promethazine hydrochloride is a racemic compound. Promethazine hydrochloride, a phenothiazine derivative, is designated chemically as 10H-Phenothiazine-10-ethanamine, N,N,Nα-trimethyl-, monohydrochloride, (±)-with the following structural formula:

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

Each tablet, for oral administration, contains 25 mg or 50 mg of promethazine hydrochloride. In addition each tablet contains the following inactive ingredients: dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose, sodium starch glycolate and stearic acid.

Promethazine Hydrochloride Tablets USP, 50 mg also contain anhydrous lactose.

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 H₁ 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
Promethazine hydrochloride tablets are 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 postoperative 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
Promethazine hydrochloride tablets are contraindicated for use in pediatric patients less than two years of age.

Promethazine hydrochloride tablets 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.

CNS Depression
Promethazine hydrochloride tablets 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
Promethazine hydrochloride tablets may lead to potentially fatal respiratory depression.

Use of promethazine hydrochloride tablets in patients with compromised respiratory function (e.g., COPD, sleep apnea) should be avoided.

Lower Seizure Threshold
Promethazine hydrochloride tablets may lower seizure threshold. They 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
Promethazine hydrochloride tablets should be used with caution in patients with bone-marrow depression. Leukopenia and agranulocytosis have been reported, usually when 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
PROMETHAZINE HYDROCHLORIDE TABLETS USP ARE CONTRAINDICATED FOR USE IN PEDIATRIC PATIENTS LESS THAN TWO YEARS OF AGE.

CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PROMETHAZINE HYDROCHLORIDE TABLETS 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 UNCOMPPLICATED VOMITING IN PEDIATRIC PATIENTS, AND THEIR USE SHOULD BE LIMITED TO PROLONGED VOMITING OF KNOWN ETIOLOGY. THE EXTRAPYRAMIDAL SYMPTOMS WHICH CAN OCCUR SECONDARY TO PROMETHAZINE HYDROCHLORIDE TABLETS ADMINISTRATION MAY BE CONFUSED WITH THE CNS SIGNS OF UNDIAGNOSED PRIMARY DISEASE, e.g., ENCEPHALOPATHY OR REYE’S SYNDROME. THE USE OF PROMETHAZINE HCI TABLETS 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 promethazinie hydrochloride tablets, in pediatric patients may cause sudden death (see OVERDOSAGE). Hallucinations and convulsions have occurred with therapeutic doses and overdoses of promethazine 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.

Promethazine hydrochloride tablets should be used cautiously in persons with cardiovascular disease or with impairment of liver function.

Drug interactions
CNS Depressants - Promethazine hydrochloride tablets 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 anti-depressants, and tranquilizers; therefore, such agents should be avoided or administered in reduced dosage to patients receiving promethazine HCl. When given concomitantly with promethazine hydrochloride tablets, 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 promethazine to reverse epinephrine’s vasopressor effect, epinephrine should NOT be used to treat hypotension associated with promethazine hydrochloride tablets 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 promethazine hydrochloride tablets.

Drug/laboratory test interactions
The following laboratory tests may be affected in patients who are receiving therapy with promethazine hydrochloride:

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 promethazine hydrochloride tablets in pregnant women. Promethazine hydrochloride tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects
Promethazine hydrochloride tablets 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 promethazine 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 promethazine hydrochloride tablets, 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
PROMETHAZINE HYDROCHLORIDE TABLETS USP ARE CONTRAINDICATED FOR USE IN PEDIATRIC PATIENTS LESS THAN TWO YEARS OF AGE (see WARNINGS-Black Box Warning and Use in Pediatric Patients). Promethazine hydrochloride tablets 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 promethazine 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 promethazine hydrochloride tablets 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.
Promethazine hydrochloride 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.

Pre- and Postoperative Use

usually require 25 to 50 mg for nighttime, presurgical, or obstetrical sedation. Adults

to 25 mg promethazine hydrochloride by the oral route or by rectal suppository at bedtime will provide sedation in children. Adults

This product relieves apprehension and induces a quiet sleep from which the patient can be easily aroused. Administration of 12.5 to 25 mg promethazine hydrochloride 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

Promethazine hydrochloride 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 promethazine HCl 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. Promethazine hydrochloride tablets are contraindicated for children under 2 years of age.

**HOW SUPPLIED**
Promethazine Hydrochloride Tablets USP, 25 mg are scored, round, white tablets imprinted DAN DAN and 5307 supplied in bottles of 100 and 1000.
Promethazine Hydrochloride Tablets USP, 50 mg are unscored, round, white tablets imprinted DAN and 5319 supplied in bottles of 100.
Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure.

**Information for patients**
Promethazine hydrochloride tablets 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.
Take _tablet(s) every _hours or _times a day.
Take as directed.
Tome _tableta(s) cada _horas o _veces al dia.
Tome como indicado.
SCORED, ROUND, WHITE TABLETS IMPRINTED DAN DAN AND 5307