Promethazine as hydrochloride

CLINICAL PHARMACOLOGY
Promethazine hydrochloride injection is a phenothiazine derivative which possesses antihistaminic, sedative, antimotion-sickness, antiemetic, and anticholinergic effects. Promethazine is a competitive H₁ receptor antagonist, but does not block the release of histamine. Structural differences from the neuroleptic phenothiazines results in its relative lack (1/10 that of chlorpromazine) of dopamine antagonist properties. In therapeutic doses, Promethazine hydrochloride injection produces no significant effects on the cardiovascular system. Clinical effects are generally apparent within 5 minutes of an intravenous injection and within 20 minutes of an intramuscular injection. Duration of action is four to six hours, although effects may persist up to 12 hours. Promethazine hydrochloride injection is metabolized in the liver, with the sulfoxides of Promethazine and N-desmethyl Promethazine being the predominant metabolites appearing in the urine. Following intravenous administration in healthy volunteers, the plasma half-life for Promethazine has been reported to range from 9 to 16 hours. The mean plasma half-life for Promethazine after intramuscular administration in healthy volunteers has been reported to be 9.8±3.4 hours.

INDICATIONS
Promethazine hydrochloride injection is indicated for the following conditions:
1. Amelioration of allergic reactions to blood or plasma.
2. In anaphylaxis as an adjunct to epinephrine and other standard measures after the acute symptoms have been controlled.
3. For other uncomplicated allergic conditions of the immediate type when oral therapy is impossible or contraindicated.
4. For sedation and relief of apprehension and to produce light sleep from which the patient can be easily aroused.
5. Active treatment of motion sickness.
6. Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.
7. As an adjunct to analgesics for the control of postoperative pain.
8. Preoperative, postoperative, and obstetric (during labor) sedation.
9. Intravenously in special surgical situations, such as repeated bronchoscopy, ophthalmic surgery, and poor-risk patients, with reduced amounts of meperidine or other narcotic analgesic as an adjunct to anesthesia and analgesia.

DOSAGE AND ADMINISTRATION
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Do not use Promethazine hydrochloride injection if solution has developed color or contains precipitate.

To avoid the possibility of physical and/or chemical incompatibility, consult specialized literature before diluting with any injectable solution or combining with any other medication.

Do not use if there is a precipitate or any sign of incompatibility.

Important Notes on Administration
The preferred parenteral route of administration for Promethazine hydrochloride injection is by deep intramuscular injection.

The proper intravenous administration of this product is well tolerated, but use of this route is not without some hazard. Not for subcutaneous administration. Inadvertent intra-arterial injection can result in gangrene of the affected extremity. Subcutaneous injection is contraindicated, as it may result in tissue necrosis. Injection into or near a nerve may result in permanent tissue damage.
When used intravenously, Promethazine hydrochloride injection should be given in concentration no greater than 25 mg/ml at a rate not to exceed 25 mg per minute; it is preferable to inject through the tubing of an intravenous infusion set that is known to be functioning satisfactorily.

**Allergic Conditions**
The average adult dose is 25 mg. This dose may be repeated within two hours if necessary, but continued therapy, if indicated, should be via the oral route as soon as existing circumstances permit. After initiation of treatment, dosage should be adjusted to the smallest amount adequate to relieve symptoms. The average adult dose for amelioration of allergic reactions to blood or plasma is 25 mg.

**Sedation**
In hospitalized adult patients, nighttime sedation may be achieved by a dose of 25 to 50 mg of Promethazine hydrochloride injection.

**Nausea and Vomiting**
For control of nausea and vomiting, the usual adult dose is 12.5 to 25 mg, not to be repeated more frequently than every four hours. When used for control of postoperative nausea and vomiting, the medication may be administered either intramuscularly or intravenously and dosage of analgesics and barbiturates reduced accordingly.

**Preoperative and Postoperative Use**
As an adjunct to preoperative or postoperative medication, 25 to 50 mg Promethazine hydrochloride injection in adults may be combined with appropriately reduced doses of analgesics and atropine-like drugs as desired. Dosage of concomitant analgesic or hypnotic medication should be reduced accordingly.

**Obstetrics**
Promethazine hydrochloride injection in doses of 50 mg will provide sedation and relieve apprehension in the early stages of labor. When labor is definitely established, 25 to 75 mg (average dose, 50 mg) Promethazine hydrochloride injection may be given intramuscularly or intravenously with an appropriately reduced dose of any desired narcotic. If necessary, Promethazine hydrochloride injection with a reduced dose of analgesic may be repeated once or twice at four-hour intervals in the course of a normal labor. A maximum total dose of 100 mg of Promethazine hydrochloride injection may be administered during a 24-hour period to patients in labor.

**Pediatric Patients**
Promethazine hydrochloride injection is not recommended for use in pediatric patients less than 2 years of age.

In pediatric patients 2 years of age and older, the dosage should not exceed half that of the suggested adult dose. As an adjunct to premedication, the suggested dose is 0.5 mg per lb. of body weight in combination with an appropriately reduced dose of narcotic or barbiturate and the appropriate dose of an atropine-like drug. Antiemetics should not be used in vomiting of unknown etiology in pediatric patients.

**CONTRAINDICATIONS**
Promethazine hydrochloride injection is contraindicated in comatose states and in patients who have demonstrated an idiosyncrasy or hypersensitivity to Promethazine or other phenothiazines. Under no circumstances should Promethazine hydrochloride injection be given by intrarterial injection due to the likelihood of severe arterio-spasm and the possibility of resultant gangrene. Promethazine hydrochloride injection should not be given by the subcutaneous route; evidence of chemical irritation has been noted, and necrotic lesions have resulted on rare occasions following subcutaneous injection. The preferred parenteral route of administration is by deep intramuscular injection.

**WARNINGS**
**Sulfite Sensitivity**
Promethazine hydrochloride injection contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthma episodes, in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low.
Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

**CNS Depression**
Promethazine hydrochloride injection may impair the mental and 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, sedative/hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tricyclic antidepressants and tranquilizers. Therefore, such agents should either be eliminated or given in reduced dosage in the presence of Promethazine HCl.

**Respiratory Depression**
Promethazine injection may lead to potentially fatal respiratory depression.

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

**Lower Seizure Threshold**
Promethazine hydrochloride injection may lower seizure threshold and 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 injection should be used with caution in patients with bone-marrow depression. Leukopenia and agranulocytosis have been reported, usually when Promethazine 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 injection is not recommended for use in pediatric patients less than two years of age.

Caution should be exercised when administering Promethazine injection to pediatric patients 2 years of age and older because of the potential for fatal respiratory depression. 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 Promethazine hydrochloride injection administration may be confused with the CNS signs of undiagnosed primary disease, e.g., encephalopathy or Reye’s syndrome.

The use of Promethazine hydrochloride injection 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 Promethazine hydrochloride injection,
Visual Inspection
This product is light sensitive and should be inspected before use and discarded if either color or particulate is observed.

Other Considerations
Sedative drugs or CNS depressants should be avoided in patients with a history of sleep apnea. Administration of Promethazine 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 injection should be used cautiously in persons with cardiovascular disease or impairment of liver function.

Information for Patients
Promethazine hydrochloride injection may cause marked drowsiness or impair the mental or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The use of alcohol, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc, with Promethazine hydrochloride injection may enhance impairment. 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. Persistent or worsening pain or burning at the injection site should be reported immediately. Avoid prolonged exposure to the sun.

Drug Interactions
CNS Depressants
Promethazine hydrochloride injection may increase, prolong, or intensify the sedative action of central-nervous-system depressants, such as alcohol, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. When given concomitantly with
other animal or human data concerning carcinogenicity, mutagenicity, or impairment of fertility. Promethazine hydrochloride injection was nonmutagenic in the Ames Salmonella test system.

**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 (approximately 2.1 and 4.2 times the maximum recommended human daily dose) of pro-Promethazine hydrochloride injection. Daily doses of 25 mg/kg intraperitoneally have been found to produce fetal mortality in rats. There are no adequate and well-controlled studies of Promethazine hydrochloride injection in pregnant women. Because animal reproduction studies are not always predictive of human response, Promethazine hydrochloride injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Adequate studies to determine the action of the drug on parturition, lactation and development of the animal neonate have not been conducted.

**Nonteratogenic Effects**

Promethazine hydrochloride injection received within two weeks of delivery may inhibit platelet aggregation in the newborn.

**Laboratory Test Interactions**

The following laboratory tests may be affected in patients who are receiving therapy with Promethazine hydrochloride injection:

- **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 glucose tolerance has been reported in patients receiving Promethazine hydrochloride injection.

**Carcinogenesis, Mutagenesis and Impairment of Fertility**

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

Signs and symptoms of overdosage range from mild depression of the central nervous system and cardiovascular system to profound hypotension, respiratory depression, and unconsciousness. Stimulation may be evident, especially in pediatric patients and geriatric patients. Convulsions may rarely occur. A paradoxical reaction has been reported in pediatric patients receiving single doses of 75 mg to 125 mg orally, characterized by hyperexcitability and nightmares.

**Side Effects**

**Central Nervous System Effects**

Drowsiness is the most prominent CNS effect of the drug. Sedation, somnolence, blurred vision, dizziness, confusion, disorientation, and Extrapyramidal symptoms such as oculogyric crisis, torticolitis, 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. Venous thromboembolism at the injection site has been reported. Intra-arterial injection may result in gangrene of the affected extremity.

**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).

**Other:** Angioneurotic edema. Neuroleptic malignant syndrome (potentially fatal) has also been reported. Subcutaneous injection has restrained in tissue necrosis Paradoxical Reactions (Overdosage) Hyperexcitability and abnormal movements, which have been reported in pediatric patients following a single administration of Promethazine hydrochloride injection, may be manifestations of relative overdosage, in which case, consideration should be given to the discontinuation of proPromethazine hydrochloride injection and to the use of other drugs. Respiratory depression, nightmares, delirium, and agitated behavior have also been reported in some of these patients.

**Pediatric Use**

Safety and effectiveness in pediatric patients under 2 years of age have not been established. Promethazine hydrochloride injection should be used with caution in pediatric patients 2 years of age and older.

**Use in Geriatric Patients (approximately 60 years or older).**

Since therapeutic requirements for sedative drugs tend to be less in geriatric patients, the dosage should be reduced for these patients.

**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. 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 hydrochloride injection 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 levarterenol or phenylephrine should be considered.
EPINEPHRINE SHOULD NOT BE USED, since its use in a patient with partial adrenergic blockade may further lower the blood pressure. Extrapyramidal reactions may be treated with anticholinergic antiparkinson agents, diphenhydramine, or barbiturates. Oxygen may also be administered. Limited experience with dialysis indicates that it is not helpful.

STORAGE
Store below 25°C, away from light.

PRESENTATIONS
Ampoules:
Promethazine Hikma 50mg: Promethazine as hydrochloride 50mg/2ml
Excepients: Glacial acetic acid, sodium acetate trihydrate, edetate disodium, sodium metabisulphite, water for injection.