CENTER FOR DRUG EVALUATION AND RESEARCH

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PROMETHAZINE HYDROCHLORIDE Injection, USP

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APPROVED

DESCRIPTION

Promethazine HCl (10*H*-Phenothiazine-10-ethanamine, *N,N,*α-trimethyl-, monohydrochloride, (±)-) has the following structural formula:

Each mL contains either 25 or 50 mg promethazine hydrochloride with 0.1 mg edetate disodium, 0.04 mg calcium chloride, not more than 5 mg monothioglycerol and 5 mg phenol with sodium acetate-acetic acid buffer. pH 4.9 (4.0 to 5.5).

ACTIONS

Promethazine hydrochloride, a phenothiazine derivative, possesses antihistaminic, sedative, antimotion-sickness, antiemetic, and anticholinergic effects. The duration of action is generally from four to six hours. The major side reaction of this drug is sedation. As an antihistamine, it acts by competitive antagonism but does not block the release of histamine. It antagonizes in varying degrees most but not all of the pharmacological effects of histamine.

INDICATIONS

The injectable form of promethazine hydrochloride 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. Active treatment of motion sickness.
5. Preoperative, postoperative, and obstetric (during labor) sedation.
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. For sedation and relief of apprehension and to produce light sleep from which the patient can be easily aroused.
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.

CONTRAINDICATIONS

Promethazine is contraindicated in comatose states, in patients who have received large amounts of central-nervous-system depressants (alcohol, sedative hypnotics, including barbiturates, general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc.), and in patients who have demonstrated an idiosyncrasy or hypersensitivity to promethazine.

Under no circumstances should promethazine be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene (see **"WARNINGS"**).

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

Promethazine 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 concomitant use of alcohol, sedative hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers or other central-nervous-system depressants may have an additive sedative effect. Patients should be warned accordingly.

Usage in Pregnancy

The safe use of promethazine has not been established with respect to the possible adverse effects upon fetal development. Therefore, the need for the use of this drug during pregnancy should be weighed against the possible but unknown hazards to the developing fetus.

Use in Pediatric Patients

Excessively large dosages of antihistamines, including promethazine, in pediatric patients may cause hallucinations, convulsions, and sudden death. In pediatric patients who are acutely ill associated with dehydration, there is an increased susceptibility to dystonias with the use of promethazine hydrochloride injection.

CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PROMETHAZINE TO 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 PROMETHAZINE ADMINISTRATION MAY BE CONFUSED WITH THE CNS SIGNS OF UNDIAGNOSED PRIMARY DISEASE, e.g., ENCEPHALOPATHY OR REYE'S SYNDROME. THE USE OF PROMETHAZINE SHOULD BE AVOIDED IN PEDIATRIC PATIENTS WHOSE SIGNS AND SYMPTOMS MAY SUGGEST REYE'S SYNDROME, OR OTHER HEPATIC DISEASES.

Use in Geriatric Patients (APPROXIMATELY 60 YEARS OR OLDER)

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

Other Considerations

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

Promethazine 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 toxic agents.

Inadvertent Intra-Arterial Injection

Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. Reports compatible with inadvertent intra-arterial injection of promethazine, usually in conjunction with other drugs intended for intravenous use, suggest that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances. Intravenous injection was intended in all the cases reported, but perivascular extravasation or arterial placement of the needle is now suspect. There is no proven successful management of this condition after it occurs, although sympathetic block and heparinization are commonly employed during the acute management because of the results of animal experiments with other known arteriolar irritants. Aspiration of dark blood does not preclude intra-arterial needle placement, because blood is discolored upon contact with promethazine. Use of syringes with rigid plungers or of small bore needles might obscure typical arterial backflow if this is relied upon alone.

When used intravenously, promethazine hydrochloride should be given in a concentration no greater than 25 mg per mL and at a rate not to exceed 25 mg per minute. When administering any irritant drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily. In the event that a patient complains of pain during intended intravenous injection of promethazine, the injection should immediately be stopped to provide for evaluation of possible arterial placement or perivascular extravasation.

PRECAUTIONS

Promethazine may significantly affect the actions of other drugs. It 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 promethazine hydrochloride, 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 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. Promethazine should be used cautiously in persons with cardiovascular disease or impairment of liver function.

Although reversal of the vasopressor effect of epinephrine has not been reported with promethazine, the possibility should be considered in case of promethazine overdose.

ADVERSE REACTIONS

CNS Effects

Drowsiness is the most prominent CNS effect of this drug. Extrapyramidal reactions may occur with high doses; this is almost always responsive to a reduction in dosage. Other reported reactions include dizziness, lassitude, tinnitus, incoordination, fatigue, blurred vision, euphoria, diplopia, nervousness, insomnia, tremors, convulsive seizures, oculogyric crises, excitation, catatonic-like states, and hysteria.

Cardiovascular Effects

Tachycardia, bradycardia, faintness, dizziness, and increases and decreases in blood pressure have been reported following the use of promethazine hydrochloride injection. Venous thrombosis at the injection site has been reported. INTRA-ARTERIAL INJECTION MAY RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (see **"WARNINGS"**).

Gastrointestinal

Nausea and vomiting have been reported, usually in association with surgical procedures and combination drug therapy.

Allergic Reactions

These include urticaria, dermatitis, asthma, and photosensitivity. Angioneurotic edema has been reported.

Other Reported Reactions

Leukopenia and agranulocytosis, usually when promethazine has been used in association with other known toxic agents, have been reported. Thrombocytopenic purpura and jaundice of the obstructive type have been associated with the use of promethazine. The jaundice is usually reversible on discontinuation of the drug. Subcutaneous injection has resulted in tissue necrosis. Nasal stuffiness may occur. Dry mouth has been reported.

Laboratory Tests

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 glucose tolerance has been reported in patients receiving promethazine hydrochloride.

Paradoxical Reactions (Overdosage)

Hyperexcitability and abnormal movements, which have been reported in pediatric patients following a single administration of promethazine, may be manifestations of relative overdosage, in which case, consideration should be given to the discontinuation of the promethazine and to the use of other drugs. Respiratory depression, nightmares, delirium, and agitated behavior have also been reported in some of these patients.

DRUG INTERACTIONS

Narcotics and Barbiturates

The CNS-depressant effects of narcotics are additive with promethazine hydrochloride.

Monoamine Oxidase Inhibitors (MAOI)

Drug interactions, including an increased incidence of extrapyramidal effects, have been reported when some MAOI and phenothiazines are used concomitantly. Although such a reaction has not been reported with promethazine, the possibility should be considered.

DOSAGE AND ADMINISTRATION

The preferred parenteral route of administration for promethazine hydrochloride 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.

INADVERTENT INTRA-ARTERIAL INJECTION CAN RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (see **"WARNINGS"**). SUBCUTANEOUS INJECTION IS CONTRAINDICATED, AS IT MAY RESULT IN TISSUE NECROSIS (see **"CONTRAINDICATIONS"**). When used intravenously, promethazine hydrochloride 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.

The Carpuject® Blunt Cannula Sterile Cartridge Unit is suitable for substances to be administered intravenously only. It is intended for use with injection sets specifically manufactured as "needle-less" injection systems. As of the date of this insert, the Carpuject Blunt Cannula is compatible with LifeShield® Prepierced Reseal Injection Site, InterLink® Injection Site, SafeLine® Injection Site, User-Gard® Intermittent Injection Cap, and SafSite® reflux valve*.

The Carpuject® Sterile Cartridge-Needle Unit and Carpuject® with Luer Lock is suitable for substances to be administered intravenously or intramuscularly.

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.

Pre- and Postoperative Use
As an adjunct to pre- or postoperative medication, 25 to 50 mg of promethazine hydrochloride 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.

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.

Obstetrics
Promethazine hydrochloride 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 may be given intramuscularly or intravenously with an appropriately reduced dose of any desired narcotic. Amnesic agents may be administered as necessary. If necessary, promethazine hydrochloride 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 may be administered during a 24-hour period to patients in labor.

Pediatric Patients
In pediatric patients under the age of 12 years, 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 equal 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.

MANAGEMENT OF 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 and geriatric patients. Atropine-like signs and symptoms – dry mouth, fixed, dilated pupils, flushing, etc., as well as gastrointestinal symptoms, may occur. The treatment of overdosage is essentially symptomatic and supportive. Early gastric lavage may be beneficial if promethazine has been taken orally. Centrally acting emetics are of little use.

Avoid analeptics, which may cause convulsions. Severe hypotension usually responds to the administration of levarterenol or phenylephrine. EPINEPHRINE SHOULD NOT BE USED, since its use in a patient with partial adrenergic blockage may further lower the blood pressure. Extrapyramidal reactions may be treated with anticholinergic antiparkinson agents, diphenhydramine, or barbiturates. Additional measures include oxygen and intravenous fluids. Limited experience with dialysis indicates that it is not helpful.

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

HOW SUPPLIED

Promethazine Hydrochloride Injection, USP is available in the following package configurations:

List	Container	Concentration	Fill	Quantity
For Intravenous or Intramuscular use:				
2312	Carpuject® (22-gauge, 1¼" needle)	25 mg/mL	1 mL	Box of 10
2312	Carpuject with Luer Lock	25 mg/mL	1 mL	Box of 10
For Intravenous use only:				
2312	Carpuject with Blunt Cannula*	25 mg/mL	1 mL	Box of 10
For Intramuscular use only:				
2335	Carpuject (22-gauge, 1¼" needle)	50 mg/mL	1 mL	Box of 10
2335	Carpuject with Luer Lock	50 mg/mL	1 mL	Box of 10

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room Temperature].

Protect from light.

Retain in carton until time of use.

Do not use if solution is discolored or contains a precipitate.

* Promethazine Hydrochloride Injection in the Blunt Cannula configuration is not intended for intramuscular (IM) use.

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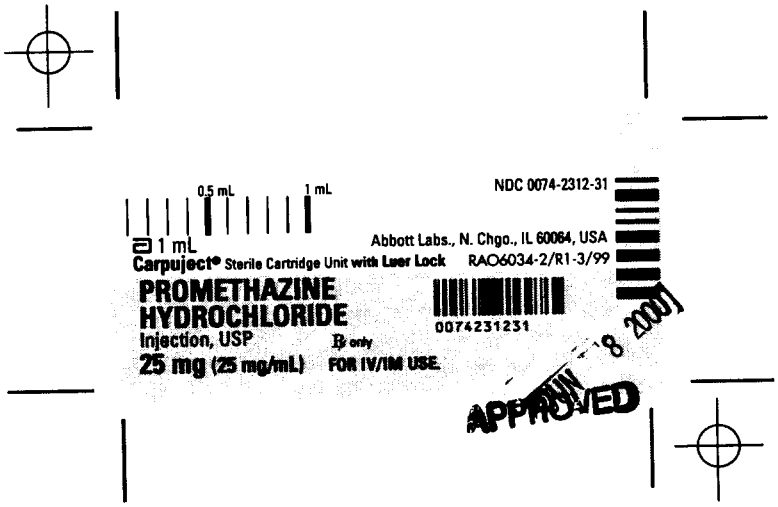
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