

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 40-454/S-006

Name: Promethazine Hydrochloride Injection USP,
25 mg/mL and 50 mg/mL.

Sponsor: TEVA Parenteral Medicines, Inc.

Approval Date: October 20, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 40-454/S-006

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 40-454/S-006

APPROVAL LETTER



ANDA 40-454/S-006

Teva Parenteral Medicines, Inc
Attention: Sunni Churchill
19 Hughes
Irvine, CA 92618

Dear Sir/Madam:

This is in reference to your supplemental new drug application dated October 15, 2009 submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug application for Promethazine Hydrochloride Injection USP, 25 mg/mL and 50 mg/mL.

Reference is also made to an FDA letter dated September 16, 2009 notifying you, under Section 505(o)(4) of the FDCA, of new safety information that should be incorporated in the labeling in the form of changes to the prescribing information, including the current boxed warning regarding the risk of respiratory depressions with promethazine hydrochloride injection, so that all of the safety information can be effectively communicated.

Your supplemental application provides for the revisions to the package insert, carton, and container labeling for Promethazine Hydrochloride Injection USP, 25 mg/mL and 50 mg/mL, consistent with our September 16, 2009 letter.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

ANDA-40454

SUPPL-6

TEVA
PARENTERAL
MEDICINES INC

PROMETHAZINE
HYDROCHLORIDE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN F GRACE
10/20/2009
for Wm Peter Rickman

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 40-454/S-006

LABELING

TEVA

NDC 0703-2191-01 Rx only

**Promethazine
Hydrochloride
Injection, USP**

25 mg/mL

FOR DEEP IM OR IV USE

1 mL Single Dose Vial

PROTECT FROM LIGHT

Teva Parenteral Medicines, Inc.
Irvine, CA 92618



YXXXXX

TEVA

NDC 0703-2201-01

Rx only

**Promethazine
Hydrochloride
Injection, USP**

50 mg/mL

FOR DEEP IM USE ONLY

1 mL Single Dose Vial

PROTECT FROM LIGHT

Teva Parenteral Medicines, Inc.
Irvine, CA 92618



YXXXXXX

NDC 0703-2191-04

Rx only

Promethazine Hydrochloride Injection, USP

25 mg/mL

**FOR DEEP INTRAMUSCULAR
OR INTRAVENOUS USE**

1 mL Single Dose Vials
25 Vials

Each mL contains: Promethazine hydrochloride 25 mg, edetate disodium 0.1 mg, calcium chloride 0.04 mg, sodium metabisulfite 0.25 mg and phenol 5 mg in water for injection. pH 4.0–5.5; buffered with acetic acid-sodium acetate. Sealed under nitrogen.

Usual Dosage:

See Package Insert.

PROTECT FROM LIGHT:

Keep covered in carton until time of use.

Store at room temperature

20°–25°C (68°–77°F)

[See USP Controlled Room Temperature].

Teva Parenteral Medicines, Inc.
Irvine, CA 92618

*LOT/EXP CODE
PLACE HOLDER
(NO TEXT)
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YXXXXX

TEVA

NDC 0703-2201-04

Rx only

Promethazine Hydrochloride Injection, USP

50 mg/mL

**FOR DEEP INTRAMUSCULAR
USE ONLY**

1 mL Single Dose Vials
25 Vials

TEVA

Each mL contains: Promethazine hydrochloride 50 mg, edetate disodium 0.1 mg, calcium chloride 0.04 mg, sodium metabisulfite 0.25 mg and phenol 5 mg in water for injection. pH 4.0–5.5; buffered with acetic acid–sodium acetate. Sealed under nitrogen.

Usual Dosage:

See Package Insert.

PROTECT FROM LIGHT:

Keep covered in carton until time of use.

Store at room temperature

20°–25°C (68°–77°F)

[See USP Controlled Room Temperature].

Teva Parenteral Medicines, Inc.
Irvine, CA 92618

*LOT/EXP CODE
PLACE HOLDER
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YXXXXX

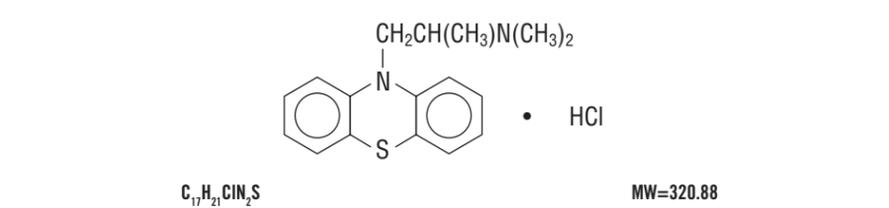
Promethazine Hydrochloride Injection, USP

TEVA

WARNINGS
RESPIRATORY DEPRESSION-<i>Pediatrics</i>
Promethazine hydrochloride injection should not be used in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression. Post-marketing cases of respiratory depression, including fatalities, have been reported with use of promethazine in pediatric patients less than 2 years of age. Caution should be exercised when administering promethazine hydrochloride injection to pediatric patients 2 years of age and older (see WARNINGS-Respiratory Depression).
SEVERE TISSUE INJURY, INCLUDING GANGRENE
Promethazine hydrochloride injection can cause severe chemical irritation and <u>damage to tissue regardless of the route of administration</u>. Irritation and damage can result from perivascular extravasation, unintentional intra-arterial injection, and intraneuronal or perineuronal infiltration. Adverse reactions include burning, pain, thrombophlebitis, tissue necrosis, and gangrene. In some cases, surgical intervention, including fasciotomy, skin graft and/or amputation have been required (see WARNINGS-Severe Tissue Injury, Including Gangrene).
Due to the risks of intravenous injection, the preferred route of administration of promethazine hydrochloride injection is deep intramuscular injection. Subcutaneous injection is contraindicated. See DOSAGE AND ADMINISTRATION for important notes on administration.

DESCRIPTION

Promethazine hydrochloride injection, USP is a sterile, pyrogen-free solution for deep intramuscular or intravenous administration. Promethazine hydrochloride (10*H*-Phenothiazine-10-ethanamine,*N,N*, α -trimethyl-, monohydrochloride, (±)-) is a racemic compound and has the following structural formula:



Each mL contains promethazine hydrochloride, either 25 mg or 50 mg, edetate disodium 0.1 mg, calcium chloride 0.04 mg, sodium metabisulfite 0.25 mg and phenol 5 mg in Water for Injection. pH 4.0 to 5.5; buffered with acetic acid-sodium acetate.

Promethazine hydrochloride injection is a clear, colorless solution. The product is light sensitive. It should be inspected before use and discarded if either color or particulate is observed.

CLINICAL PHARMACOLOGY

Promethazine hydrochloride 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 result in its relative lack (1/10 that of chlorpromazine) of dopamine antagonist properties. 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 is metabolized in the liver, with the sulfoxides of promethazine and N-desmethylpromethazine 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 AND USAGE

Promethazine hydrochloride injection is indicated for the following conditions:

- Amelioration of allergic reactions to blood or plasma.
- In anaphylaxis as an adjunct to epinephrine and other standard measures after the acute symptoms have been controlled.
- For other uncomplicated allergic conditions of the immediate type when oral therapy is impossible or contraindicated.
- For sedation and relief of apprehension and to produce light sleep from which the patient can be easily aroused.
- Active treatment of motion sickness.
- Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.
- As an adjunct to analgesics for the control of postoperative pain.
- Preoperative, postoperative, and obstetric (during labor) sedation.
- 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

Children less than 2 years of age

Promethazine hydrochloride injection is contraindicated for use in pediatric patients less than two years of age due to the risk of respiratory depression (see **WARNINGS Respiratory Depression**).

Comatose state

Promethazine hydrochloride injection is contraindicated in comatose states.

Intra-arterial injection

Under no circumstances should promethazine hydrochloride injection be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene (see **WARNINGS—Severe Tissue Injury, Including Gangrene**).

Subcutaneous injection

Promethazine hydrochloride injection should not be given by the subcutaneous route; because evidence of chemical irritation has been noted, and necrotic lesions have resulted following subcutaneous injection. The preferred parenteral route of administration is by deep intramuscular injection.

Idiosyncratic reaction or hypersensitivity

Promethazine hydrochloride injection is contraindicated in patients who have demonstrated an idiosyncratic reaction or hypersensitivity to promethazine or other phenothiazines.

WARNINGS

Respiratory Depression

Pediatrics

Promethazine hydrochloride injection should not be used in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression. Post-marketing cases of respiratory depression, including fatalities, have been reported with use of promethazine in pediatric patients less than 2 years of age. A wide range of weight-based doses of promethazine hydrochloride injection have resulted in respiratory depression in these patients.

Caution should be exercised when administering promethazine hydrochloride injection to pediatric patients 2 years of age and older. It is recommended that the lowest effective dose of promethazine hydrochloride injection be used in pediatric patients 2 years of age and older. Avoid concomitant administration of other drugs with respiratory depressant effects because of an association with respiratory depression, and sometimes death, in pediatric patients.

Other

Because of the risk of potentially fatal respiratory depression, use of promethazine hydrochloride injection in patients with compromised respiratory function or patients at risk for respiratory failure (e.g. COPD, sleep apnea) should be avoided.

Severe Tissue Injury, Including Gangrene

Promethazine hydrochloride injection can cause severe chemical irritation and damage to tissues regardless of the route of administration. Irritation and damage can result from perivascular extravasation, unintentional intra-arterial injection, and intraneuronal or perineuronal infiltration. Adverse event reports include burning, pain, erythema, swelling, sensory loss, palsies, paralysis, severe spasm of distal vessels, thrombophlebitis, venous thrombosis, phlebitis, abscesses, tissue necrosis, and gangrene. In some cases, surgical intervention, including fasciotomy, skin graft, and/ or amputation have been required.

Because of the risks of intravenous injection, the preferred route of administration of promethazine hydrochloride injection is deep intramuscular injection (see **DOSAGE AND ADMINISTRATION). Subcutaneous injection is contraindicated. 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 unintentional intra-arterial injection as pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances. Aspiration of dark blood does not preclude intra-arterial needle placement because blood is discolored upon contact with promethazine hydrochloride injection. Use of syringes with rigid plungers or of small-bore needles might obscure typical arterial backflow if this is relied upon alone.**

In the event that a patient complains of pain during intravenous injection of promethazine hydrochloride injection, the injection should be stopped immediately to evaluate for possible arterial injection or perivascular extravasation.

There is no proven successful management of unintentional intra-arterial injection or perivascular extravasation after it occurs. Sympathetic block and heparinization have been employed during the acute management of unintentional intraarterial injection, because of the results of animal experiments with other arteriolar irritants.

CNS Depression

Promethazine hydrochloride injection 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, 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 hydrochloride (see **PRECAUTIONS—Information for Patients and Drug Interactions**).

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 hydrochloride 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 hydrochloride 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 hydrochloride, 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 hydrochloride should be carefully considered.

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.

Visual Inspection

This product is light sensitive and should be inspected before use and discarded if either color or particulate is observed.

Cholestatic Jaundice

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

Patients should be advised of the risk of respiratory depression, including potentially fatal respiratory depression in children less than 2 years of age (see **WARNINGS-Respiratory Depression**).

Patients should be advised of the risk of severe tissue injury, including gangrene (see **WARNINGS-Severe Tissue Injury, Including Gangrene**). Patients should be advised to immediately report persistent or worsening pain or burning at the injection site.

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. Pediatric patients should be supervised to avoid potential harm in bike riding or in other hazardous activities. The concomitant use of alcohol, sedative/hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tricyclic antidepressants, and tranquilizers may enhance impairment (see **WARNINGS—CNS Depression** and **PRECAUTIONS—Drug Interactions**).

Patients should be advised to report any involuntary muscle movements (see **ADVERSE REACTIONS-Paradoxical Reactions**).

Patients should be advised to avoid prolonged exposure to the sun (see **ADVERSE REACTIONS-Dermatologic**).

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, tricyclic antidepressants, and tranquilizers; therefore, such agents should be avoided or administered in reduced dosage to patients receiving promethazine hydrochloride. When given concomitantly with promethazine hydrochloride injection, 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 hydrochloride injection 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 hydrochloride to reverse epinephrine's vasopressor effect, epinephrine should NOT be used to treat hypotension associated with promethazine hydrochloride injection overdose.

Anticholinergics

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

Monoamine Oxidase (MAO) Inhibitors

Drug interactions, including an increased incidence of extrapyramidal effects, have been reported when some MAO inhibitors and phenothiazines are used concomitantly. This possibility should be considered with promethazine hydrochloride injection.

Drug/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 blood glucose has been reported in patients receiving promethazine hydrochloride.

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 *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 (approximately 2.1 and 4.2 times the maximum recommended human daily dose) of 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.

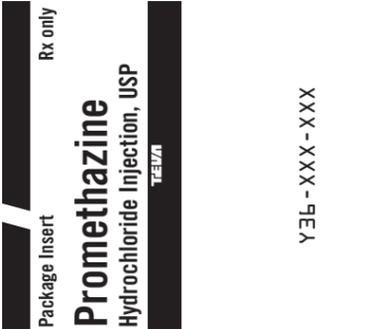
Adequate studies to determine the action of the drug on parturition, lactation and development of the animal neonate have not been conducted.

Nonteratogenic Effects

Promethazine hydrochloride injection administered to a pregnant woman within two weeks of delivery may inhibit platelet aggregation in the newborn.

Labor and Delivery

Promethazine hydrochloride injection may be used alone or as an adjunct to narcotic analgesics during labor (see **DOSAGE AND ADMINISTRATION**). Limited data suggest that use of promethazine hydrochloride injection 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 **Pregnancy—Nonteratogenic Effects**.)



XXX-XXX-PEA

Nursing Mothers

It is not known whether promethazine hydrochloride injection 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 injection, 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 injection is contraindicated for use in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression. **Promethazine hydrochloride injection should be used with caution in pediatric patients 2 years of age and older** (see **WARNINGS-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 extrapvrnaridal 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 reve'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 dosage of antihistamines, including promethazine hydrochloride injection, in pediatric patients may cause sudden death (see **OVERDOSAGE**). Hallucinations and convulsions have occurred with therapeutic doses and overdoses of promethazine hydrochloride injection 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 hydrochloride injection.

Geriatric Use (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.

ADVERSE REACTIONS

Respiratory Depression

Promethazine hydrochloride injection is contraindicated in pediatric patients less than 2 years of age, because of the potential for fatal respiratory depression. Promethazine hydrochloride injection should be used with caution in pediatric patients 2 years of age and older (see **WARNINGS-Respiratory Depression**).

Severe Tissue Injury, including Gangrene

Promethazine hydrochloride injection can cause severe chemical irritation and damage to tissues regardless of the route of administration. Irritation and damage can result from perivascular extravasation, unintentional intra-arterial injection and intraneuronal or perineuronal infiltration. Adverse reactions include burning, pain, erythema, swelling, sensory loss, palsies, paralysis, severe spasm of distal vessels, thrombophlebitis, venous thrombosis, phlebitis, abscesses, tissue necrosis, and gangrene. In some cases, surgical intervention, including fasciotomy, skin graft, and/ or amputation have been required (see **WARNINGS-Severe Tissue Injury, Including Gangrene**; and **DOSAGE AND ADMINISTRATION**).

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 hydrochloride injection. Consideration should be given to the discontinuation of promethazine hydrochloride injection 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 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 pediatric patients and geriatric patients. Convulsions may rarely occur. A paradoxical-type reaction has been reported in pediatric patients 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; etc, 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. 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 norepinephrine 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. Extrapramidal 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.

DOSAGE AND ADMINISTRATION

Important Notes on Administration

Promethazine hydrochloride injection can cause severe chemical irritation and **damage to tissues regardless of the route of administration**. Irritation and damage can result from perivascular extravasation, unintentional intra-arterial injection, and intraneuronal or perineuronal infiltration (see **WARNINGS-Severe Tissue Injury, Including Gangrene**).

- The preferred parenteral route of administration for promethazine hydrochloride injection is by deep intramuscular injection.**
- Under no circumstances should promethazine hydrochloride injection be given by intra-arterial injection due to likelihood of severe arteriospasm and the possibility of resultant gangrene (see **WARNINGS-Severe Tissue Injury, Including Gangrene**).
- Subcutaneous injection is contraindicated as it may result in tissue necrosis.
- When administered intravenously, promethazine hydrochloride injection should be given in a concentration no greater than 25 mg per mL and 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.

- In the event that a patient complains of pain during intravenous injection of promethazine hydrochloride injection, the injection should be stopped immediately to evaluate for possible arterial injection or perivascular extravasation.

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.

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 should be reduced accordingly. (see **PRECAUTIONS-Drug Interactions**).

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

Preoperative and Postoperative Use

As an adjunct to preoperative or postoperative medication, 25 to 50 mg of 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.(see **PRECAUTIONS-Drug Interactions**.)

Promethazine hydrochloride is contraindicated for use in pediatric patients less than two years of age.

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. (see **PRECAUTIONS-Drug Interactions**.) 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 contraindicated for use in pediatric patients less than 2 years of age (see WARNINGS-Respiratory Depression). Caution should be exercised when administering promethazine hydrochloride injection to pediatric patients 2 years of age or older. It is recommended that the lowest effective dose of promethazine hydrochloride be used in pediatric patients 2 years of age and older and concomitant administration of other drugs with respiratory depressant effects be avoided (see WARNINGS-Respiratory Depression).

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 1.1 mg per kg of body weight in combination with an appropriately reduced dose of narcotic or barbiturate and the appropriate dose of an atropine-like drug. (see **PRECAUTIONS-Drug Interactions**.) Antiemetics should not be used in vomiting of unknown etiology in pediatric patients.

HOW SUPPLIED

Promethazine hydrochloride injection, USP is available as follows:

NDC Number	Strength	Package
0703-2191-04	25 mg/mL	1 mL fill in a 2 mL vial 25 vial per shelf tray
0703-2201-04	50 mg/mL	1 mL fill in a 2 mL vial 25 vial per shelf tray

Store at room temperature 20°–25°C (68°–77°F) [See USP Controlled Room Temperature].

Protect from light. Keep covered in carton until time of use.

Do not use if solution has developed color or contains a precipitate.

Issued: October 2009
Manufactured by:
Teva Parenteral Medicines, Inc.
Irvine, CA 92618

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 40-454/S-006

LABELING REVIEWS

**Labeling Review Branch
Division of Labeling and Program Support
Office of Generic Drugs**

Labeling Supplement Review

Application Number: 40-454[S-006

Name of Drug: Promethazine Hydrochloride Injection USP, 25 mg/mL and 50 mg/mL

Applicant: Teva Parenteral Medicines, Inc

Material Reviewed: Package Insert, Carton, and Container Labeling

Submission Date(s): October 15, 2009

Background and Summary

1. The supplemental application provides for: Revised package insert, carton and container labeling
2. Model labeling: This is the RLD.
3. Patent/Exclusivity Statement: N/A

Review

FOR THE RECORD:

1. In a letter dated September 16, 2009, the Agency requested that Teva revise their labeling to include changes pertaining to the addition of new safety information that is incorporated in the package insert, carton, and container labeling in the form of changes to the prescribing information, including the current boxed warning, to be in accordance with the Safety Labeling Changes under section 505(o)(4) of the FDCA.
2. New information and revisions that were added to the BOXED WARNING, WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections:

The following boxed warning should appear at the beginning of the product label.

BOXED WARNING

WARNINGS

RESPIRATORY DEPRESSION – Pediatrics

Promethazine hydrochloride injection should not be used in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression. Post-marketing cases of respiratory depression, including fatalities, have been reported with use of promethazine in pediatric patients less than 2 years of age. Caution should be exercised when administering promethazine

hydrochloride injection to pediatric patients 2 years of age and older (see WARNINGS – Respiratory Depression).

SEVERE TISSUE INJURY, INCLUDING GANGRENE

Promethazine hydrochloride injection can cause severe chemical irritation and damage to tissues regardless of the route of administration. Irritation and damage can result from perivascular extravasation, unintentional intra-arterial injection, and intraneuronal or perineuronal infiltration. Adverse reactions include burning, pain, thrombophlebitis, tissue necrosis, and gangrene. In some cases, surgical intervention, including fasciotomy, skin graft, and/or amputation have been required (see WARNINGS – Severe Tissue Injury, Including Gangrene).

Due to the risks of intravenous injection, the preferred route of administration of promethazine hydrochloride injection is deep intramuscular injection. Subcutaneous injection is contraindicated. See DOSAGE AND ADMINISTRATION for important notes on administration.

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Revise the WARNINGS section to include the following changes at the beginning of the section.

WARNINGS

Respiratory Depression

Pediatrics

Promethazine hydrochloride injection should not be used in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression. Post-marketing cases of respiratory depression, including fatalities, have been reported with use of promethazine in pediatric patients less than 2 years of age. A wide range of weight-based doses of promethazine hydrochloride injection have resulted in respiratory depression in these patients.

Caution should be exercised when administering promethazine hydrochloride injection to pediatric patients 2 years of age and older. It is recommended that the lowest effective dose of promethazine hydrochloride injection be used in pediatric patients 2 years of age and older. Avoid concomitant administration of other drugs with respiratory depressant effects because of an association with respiratory depression, and sometimes death, in pediatric patients.

Other

Because of the risk of potentially fatal respiratory depression, use of promethazine hydrochloride injection in patients with compromised respiratory function or patients at risk for respiratory failure (e.g. COPD, sleep apnea) should be avoided.

Severe Tissue Injury, Including Gangrene

Promethazine hydrochloride injection can cause severe chemical irritation and damage to tissues regardless of the route of administration. Irritation and damage can result from perivascular extravasation, unintentional intra-arterial injection, and intraneuronal or perineuronal infiltration. Adverse event reports include burning, pain, erythema, swelling, sensory loss, palsies, paralysis, severe spasm of distal vessels, thrombophlebitis, venous thrombosis, phlebitis, abscesses, tissue necrosis, and gangrene. In some cases, surgical intervention, including fasciotomy, skin graft, and/or amputation have been required.

Deleted: WARNINGS¶
WARNING: PROMETHAZINE HYDROCHLORIDE INJECTION 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 PROMETHAZINE HYDROCHLORIDE INJECTION IN PEDIATRIC PATIENTS LESS THAN 2 YEARS OF AGE. A WIDE RANGE OF WEIGHT-BASED DOSES OF PROMETHAZINE HYDROCHLORIDE INJECTION HAVE RESULTED IN RESPIRATORY DEPRESSION IN THESE PATIENTS. ¶ CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PROMETHAZINE HYDROCHLORIDE INJECTION TO PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER. IT IS RECOMMENDED THAT THE LOWEST EFFECTIVE DOSE OF PROMETHAZINE HYDROCHLORIDE INJECTION BE USED IN PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER AND CONCOMITANT ADMINISTRATION OF OTHER DRUGS WITH RESPIRATORY DEPRESSANT EFFECTS BE AVOIDED.¶

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Because of the risks of intravenous injection, the preferred route of administration of promethazine hydrochloride injection is deep intramuscular injection (see DOSAGE AND ADMINISTRATION). Subcutaneous injection is contraindicated. 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 unintentional intra-arterial injection as pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances. Aspiration of dark blood does not preclude intra-arterial needle placement because blood is discolored upon contact with promethazine hydrochloride injection. Use of syringes with rigid plungers or of small-bore needles might obscure typical arterial backflow if this is relied upon alone.

In the event that a patient complains of pain during intravenous injection of promethazine hydrochloride injection, the injection should be stopped immediately to evaluate for possible arterial injection or perivascular extravasation.

There is no proven successful management of unintentional intra-arterial injection or perivascular extravasation after it occurs. Sympathetic block and heparinization have been employed during the acute management of unintentional intraarterial injection, because of the results of animal experiments with other known arteriolar irritants.

Revise the ADVERSE REACTIONS section to include the following changes.

ADVERSE REACTIONS

Respiratory Depression

Promethazine hydrochloride injection is contraindicated in pediatric patients less than 2 years of age, because of the potential for fatal respiratory depression. Promethazine hydrochloride injection should be used with caution in pediatric patients 2 years of age and older (see WARNINGS—Respiratory Depression).

Severe Tissue Injury, including Gangrene

Promethazine hydrochloride injection can cause severe chemical irritation and damage to tissues regardless of the route of administration. Irritation and damage can result from perivascular extravasation, unintentional intra-arterial injection and intraneuronal or perineuronal infiltration. Adverse reactions include burning, pain, erythema, swelling, sensory loss, palsies, paralysis, severe spasm of distal vessels, thrombophlebitis, venous thrombosis, phlebitis, abscesses, tissue necrosis, and gangrene. In some cases, surgical intervention, including fasciotomy, skin graft, and/or amputation have been required (see WARNINGS - Severe Tissue Injury, Including Gangrene; and DOSAGE AND ADMINISTRATION).

Cardiovascular

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

Other

Angioneurotic edema. Neuroleptic Malignant Syndrome (potentially fatal) has also been reported. (See WARNINGS—Neuroleptic Malignant Syndrome.)

Deleted: Respiratory Depression ¶
Promethazine hydrochloride 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. ¶

¶
Use in Pediatric Patients ¶
PROMETHAZINE HYDROCHLORIDE INJECTION IS CONTRAINDICATED FOR USE IN PEDIATRIC PATIENTS LESS THAN TWO YEARS OF AGE. ¶ CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PROMETHAZINE HYDROCHLORIDE INJECTION 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. [1]

Deleted: Excessively large dosages of antihistamines, including promethazine hydrochloride injection, in pediatric patients may cause sudden death (see OVERDOSAGE). Hallucinations and convulsions have occurred with therapeutic doses and overdoses of promethazine hydrochloride injection 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 hydrochloride inject [2]

Deleted: ¶

Deleted: Thrombophlebitis, venous thrombosis, and phlebitis at the injection site have been reported and in some cases have required surgical intervention. INTRA-ARTERIAL INJECTION MAY RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (see CONTRAINDICATIONS, WARNINGS—Injection Site Reactions, and DOSAGE AND ADMINISTRATION).

Deleted: Administration of promethazine hydrochloride injection has resulted in nerve damage ranging from temporary sensory loss to palsies and paralysis. Injection into or near a nerve may result in permanent tissue damage. Subcutaneous injection has resulted in tissue necrosis. Injection site reactions including burning, erythema, pain, and edema have been reported. Administration of promethazine hydrochloride injection has resulted in abscesses and/or tissue necrosis at [3]

Revise the DOSAGE AND ADMINISTRATION section to include the following changes at the beginning of the section.

DOSAGE AND ADMINISTRATION

Important Notes on Administration

Promethazine hydrochloride injection can cause severe chemical irritation and **damage to tissues regardless of the route of administration**. Irritation and damage can result from perivascular extravasation, unintentional intra-arterial injection, and intraneuronal or perineuronal infiltration (see **WARNINGS - Severe Tissue Injury, Including Gangrene**).

- **The preferred parenteral route of administration for promethazine hydrochloride injection is by deep intramuscular injection.**
- Under no circumstances should promethazine hydrochloride injection be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene (see **WARNINGS - Severe Tissue Injury, Including Gangrene**).
- Subcutaneous injection is contraindicated as it may result in tissue necrosis.
- **When administered intravenously, promethazine hydrochloride injection should be given in a concentration no greater than 25 mg per mL and 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.
- **In the event that a patient complains of pain during intravenous injection of promethazine hydrochloride injection, the injection should be stopped immediately to evaluate for possible arterial injection or perivascular extravasation.**

Deleted: Promethazine hydrochloride injection is contraindicated for use in pediatric patients less than 2 years of age.

3. Revisions made to the Carton and Container labeling:

Carton/Shelf Pack and Container Labeling

1. Eliminate the use of the abbreviations IM and IV. Use the words Intramuscular and Intravenous if space permits.
2. Increase the prominence of and relocate the statements FOR DEEP INTRAMUSCULAR OR INTRAVENOUS USE (on the 25 mg/mL) and FOR DEEP INTRAMUSCULAR USE ONLY (on the 50 mg/mL) to inside the color shaded boxes that currently contain the drug name, strength, and dosage form. These statements represent a significant difference between the 25mg/mL and 50 mg/mL products but currently these statements do not stand apart from less vital information. This difference needs greater prominence and should be highlighted in the same manner as the different strengths are highlighted.
3. Use different colors, boxing, or some other means to distinguish the different statements of strength, 50 mg/mL and 25 mg/mL. Currently, both statements of strength appear in the same black font. Using the same color font does not provide adequate differentiation of strengths. On the other hand, use of different contrasting colors, boxing, or some other means can minimize the potential for selection errors between the two different strengths when they are stored side-by-side or in similar locations. Ensure that the colors or boxing used provide sufficient contrast with background colors for easy readability.
4. Delete the statement, DO NOT USE IF SOLUTION HAS DEVELOPED COLOR OR CONTAINS A PRECIPITATE. Deletion of this statement, that is generally applicable to any injectable drugs, will allow more space for increased prominence of more important information.

All Carton/Shelf Pack Labeling

1. Remove the bold font from the statement, 25 Vials. Use of bold font for non- critical information undermines the utility of bold font to create emphasis on critical information. Moreover,



emphasizing '25 Vials' may lead to medication errors if a practitioner mistakenly reads the '25' in '25 Vials' as the strength when the intended selection is for the 50 mg/mL strength.

Recommendation

Approved

{see appended electronic signature}

□□□□□□□□□□

Burhan Nour
Labeling Reviewer

Supervisory Comment/Concurrence:

{see appended electronic signature}

□□□□

John Grace
Team Leader

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

ANDA-40454

SUPPL-6

TEVA
PARENTERAL
MEDICINES INC

PROMETHAZINE
HYDROCHLORIDE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BURHAN A NOUR
10/17/2009

JOHN F GRACE
10/20/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 40-454/S-006

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



October 15, 2009

Mr. Gary Buehler, Director
OGD/CDER
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

Promethazine Hydrochloride Injection, USP
25 mg/mL and 50 mg/mL
ANDA: 40-454/0000

Safety Labeling Changes Under 505(o)(4) – Prior Approval Supplement

Dear Mr. Buehler:

Reference is made to Teva Parenteral Medicine's ANDA 40-454 for Promethazine Hydrochloride Injection approved by the Agency on August 22, 2002. Further reference is made to the [FDA letter](#) sent to Teva Parenteral Medicines, Inc. dated September 16, 2009, in which the Agency requested revise our labeling with new safety information.

In accordance with the provisions of Section 314.70(b) of the Code of Federal Regulations, Title 21, we hereby supplement this application with the changes requested in the FDA letter dated September 16, 2009. We hereby submit the final printed labeling.

The new safety information has been incorporated in the prescribing information, including the boxed warning. All changes as requested in the letter have been implemented to the package insert, vial labels, and shelfpack labels respectively.

We trust you will find the information in this application satisfactory for your review and approval. If there are any questions concerning this application, please do not hesitate in contacting me at (949) 829-5429. We can also be contacted by facsimile at (949) 583-7351. Sincerely,

{See appended electronic signature page}

Sunni Churchill
Senior Manager, Regulatory Affairs
Technical Contact: Marianne Lavin, Manager, Regulatory Operations
marianne.lavin@tevausa.com
(949) 455-4794

THIS IS A REPRESENTATION OF AN ELECTRONIC RECORD THAT WAS SIGNED ELECTRONICALLY AND THIS PAGE IS THE MANIFESTATION OF THE ELECTRONIC SIGNATURE

Teva Parenteral Medicines

1-2-Cover-Letter

APPROVALS

Signed by	Meaning of Signature	Server Date
Sunni Churchill	Regulatory Affairs Approval	15-Oct-2009 05:58:25 PM



ANDA 40-454



Teva Parental Medicines, Inc.
Attn: Sunni Churchill
Regulatory Affairs
19 Hughes Street
Irvine, CA 92618-1902

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Promethazine Hydrochloride Injection USP, 25 mg/mL and 50 mg/mL, 1 mL vials.

SAFETY LABELING CHANGES

Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug product applications under section 505(j) (an abbreviated new drug application or ANDA) to make safety related label changes based upon new safety information that becomes available after approval of the drug if the same drug approved under section 505(b) is not currently marketed. You are the holder of ANDA 40-454 which references a drug approved under section 505(b) that is not currently marketed.

Since Promethazine Hydrochloride Injection, USP was approved on August 22, 2002, we have become aware of adverse event reports of severe tissue injury, including gangrene, with the use of Promethazine Hydrochloride Injection. We consider this information to be "new safety information" as defined in the Food and Drug Administration Amendments Act (FDAAA).

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above, we believe that the new safety information should be included in the labeling for Promethazine Hydrochloride Injection.

We believe that this new safety information should be incorporated in the labeling in the form of changes to the prescribing information, including the current boxed warning regarding the risk of respiratory depression with promethazine hydrochloride injection, so that all of the safety information can be effectively communicated.

We believe that the current product label should be revised to include the changes shown in the attached labeling (additions are noted by underline and deletions are noted by

~~strike through.~~ In addition, we have included at the end of the letter a list of carton and container labeling changes that we believe should also be implemented.

The following boxed warning should appear at the beginning of the product label.

BOXED WARNING

WARNINGS

RESPIRATORY DEPRESSION – *Pediatrics*

Promethazine hydrochloride injection should not be used in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression. Post-marketing cases of respiratory depression, including fatalities, have been reported with use of promethazine in pediatric patients less than 2 years of age. Caution should be exercised when administering promethazine hydrochloride injection to pediatric patients 2 years of age and older (see WARNINGS – Respiratory Depression).

SEVERE TISSUE INJURY, INCLUDING GANGRENE

Promethazine hydrochloride injection can cause severe chemical irritation and damage to tissues regardless of the route of administration. Irritation and damage can result from perivascular extravasation, unintentional intra-arterial injection, and intraneuronal or perineuronal infiltration. Adverse reactions include burning, pain, thrombophlebitis, tissue necrosis, and gangrene. In some cases, surgical intervention, including fasciotomy, skin graft, and/or amputation have been required (see WARNINGS – Severe Tissue Injury, Including Gangrene).

Due to the risks of intravenous injection, the preferred route of administration of promethazine hydrochloride injection is deep intramuscular injection. Subcutaneous injection is contraindicated. See DOSAGE AND ADMINISTRATION for important notes on administration.

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Revise the WARNINGS section to include the following changes at the beginning of the section.

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WARNINGS

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Respiratory Depression

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Pediatrics

Promethazine hydrochloride injection should not be used in pediatric patients less than 2 years of age because of the potential for fatal respiratory

depression. Post-marketing cases of respiratory depression, including fatalities, have been reported with use of promethazine in pediatric patients less than 2 years of age. A wide range of weight-based doses of promethazine hydrochloride injection have resulted in respiratory depression in these patients.

Caution should be exercised when administering promethazine hydrochloride injection to pediatric patients 2 years of age and older. It is recommended that the lowest effective dose of promethazine hydrochloride injection be used in pediatric patients 2 years of age and older. Avoid concomitant administration of other drugs with respiratory depressant effects because of an association with respiratory depression, and sometimes death, in pediatric patients.

Other

Because of the risk of potentially fatal respiratory depression, use of promethazine hydrochloride injection in patients with compromised respiratory function or patients at risk for respiratory failure (e.g. COPD, sleep apnea) should be avoided.

Severe Tissue Injury, Including Gangrene

Promethazine hydrochloride injection can cause severe chemical irritation and damage to tissues regardless of the route of administration. Irritation and damage can result from perivascular extravasation, unintentional intra-arterial injection, and intraneuronal or perineuronal infiltration. Adverse event reports include burning, pain, erythema, swelling, sensory loss, palsies, paralysis, severe spasm of distal vessels, thrombophlebitis, venous thrombosis, phlebitis, abscesses, tissue necrosis, and gangrene. In some cases, surgical intervention, including fasciotomy, skin graft, and/or amputation have been required.

Because of the risks of intravenous injection, the preferred route of administration of promethazine hydrochloride injection is deep intramuscular injection (see DOSAGE AND ADMINISTRATION). Subcutaneous injection is contraindicated. 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 unintentional intra-arterial injection as pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances. Aspiration of dark blood does not preclude intra-arterial needle placement because blood is discolored upon contact with promethazine hydrochloride injection. Use of syringes with rigid plungers or of small-bore needles might obscure typical arterial backflow if this is relied upon alone.

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In the event that a patient complains of pain during intravenous injection of promethazine hydrochloride injection, the injection should be stopped immediately to evaluate for possible arterial injection or perivascular extravasation.

There is no proven successful management of unintentional intra-arterial injection or perivascular extravasation after it occurs. Sympathetic block and heparinization have been employed during the acute management of unintentional intraarterial injection, because of the results of animal experiments with other known arteriolar irritants.

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Revise the ADVERSE REACTIONS section as follows:

ADVERSE REACTIONS

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Respiratory Depression

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Promethazine hydrochloride injection is contraindicated in pediatric patients less than 2 years of age, because of the potential for fatal respiratory depression. Promethazine hydrochloride injection should be used with caution in pediatric patients 2 years of age and older (see **WARNINGS—Respiratory Depression**).

Severe Tissue Injury, including Gangrene

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Promethazine hydrochloride injection can cause severe chemical irritation and damage to tissues regardless of the route of administration. Irritation and damage can result from perivascular extravasation, unintentional intra-arterial injection and intraneuronal or perineuronal infiltration. Adverse reactions include burning, pain, erythema, swelling, sensory loss, palsies, paralysis, severe spasm of distal vessels, thrombophlebitis, venous thrombosis, phlebitis, abscesses, tissue necrosis, and gangrene. In some cases, surgical intervention, including fasciotomy, skin graft, and/or amputation have been required (see **WARNINGS—Severe Tissue Injury, Including Gangrene; and DOSAGE AND ADMINISTRATION**).

Cardiovascular

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

Other

Angioneurotic edema. Neuroleptic Malignant Syndrome (potentially fatal) has also been reported. (See **WARNINGS—Neuroleptic Malignant Syndrome**.)

Revise the DOSAGE AND ADMINISTRATION section to include the following changes at the beginning of the section.

DOSAGE AND ADMINISTRATION

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Important Notes on Administration

Promethazine hydrochloride injection can cause severe chemical irritation and damage to tissues regardless of the route of administration. Irritation and damage can result from perivascular extravasation, unintentional intra-arterial injection, and intraneuronal or perineuronal infiltration (see **WARNINGS – Severe Tissue Injury, Including Gangrene**).

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- **The preferred parenteral route of administration for promethazine hydrochloride injection is by deep intramuscular injection.**
- Under no circumstances should promethazine hydrochloride injection be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene (see **WARNINGS – Severe Tissue Injury, Including Gangrene**).
- Subcutaneous injection is contraindicated as it may result in tissue necrosis.
- **When administered intravenously, promethazine hydrochloride injection should be given in a concentration no greater than 25 mg per mL and 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.
- In the event that a patient complains of pain during intravenous injection of promethazine hydrochloride injection, the injection should be stopped immediately to evaluate for possible arterial injection or perivascular extravasation.

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Carton/Shelf Pack and Container Labeling

1. Avoid the use of the abbreviations IM and IV. Use the words Intramuscular and Intravenous if space permits.
2. Increase the prominence of and relocate the statements FOR DEEP INTRAMUSCULAR OR INTRAVENOUS USE (on the 25 mg/mL) and FOR DEEP INTRAMUSCULAR USE ONLY (on the 50 mg/mL) to inside the color shaded boxes that currently contain the drug name, strength, and dosage form. These statements represent a significant difference between the 25mg/mL and 50 mg/mL products but currently these statements do not stand apart from less vital information. This difference needs greater prominence and should be highlighted in the same manner as the different strengths are highlighted.
3. Use different colors, boxing, or some other means to distinguish the different statements of strength, 50 mg/mL and 25 mg/mL. Currently, both statements of strength appear in the same black font. Using the same color font does not provide adequate differentiation of strengths. Use of different contrasting colors, boxing, or some other means can minimize the potential for selection errors between the two different strengths when they are stored side-by-side or in similar locations. Ensure that the colors or boxing used provide sufficient contrast with background colors for easy readability.

4. Delete the statement, DO NOT USE IF SOLUTION HAS DEVELOPED COLOR OR CONTAINS A PRECIPITATE. Deletion of this statement, that is generally applicable to any injectable drug, will allow more space for increased prominence of more important information.

All Carton/Shelf Pack Labeling

1. Remove the bold font from the statement, 25 Vials. Use of bold font for non- critical information undermines the utility of bold font to create emphasis on critical information. Moreover, emphasizing '25 Vials' may lead to medication errors if a practitioner mistakenly reads the '25' in '25 Vials' as the strength when the intended selection is for the 50 mg/mL strength.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior approval supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted. Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT
OR
SAFETY LABELING CHANGES UNDER 505(o)(4) - CHANGE NOT WARRANTED

Include labeling in Final Printed Labeling (FPL) and Microsoft Word format .
If you do not submit electronically, please send 5 copies of the submission.

If you have any questions, contact Burhan Nour, Labeling Reviewer at (240) 276-8990 or burhan.nour@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure: Package Insert

Promethazine Hydrochloride Injection, USP

Rx only

WARNINGS

RESPIRATORY DEPRESSION – Pediatrics

Promethazine hydrochloride injection should not be used in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression. Post-marketing cases of respiratory depression, including fatalities, have been reported with use of promethazine in pediatric patients less than 2 years of age. Caution should be exercised when administering promethazine hydrochloride injection to pediatric patients 2 years of age and older (see WARNINGS – Respiratory Depression).

SEVERE TISSUE INJURY, INCLUDING GANGRENE

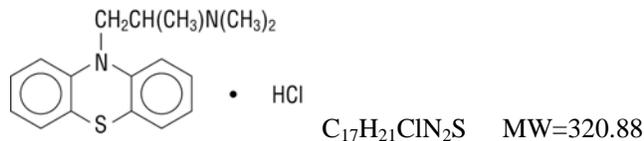
Promethazine hydrochloride injection can cause severe chemical irritation and damage to tissues regardless of the route of administration. Irritation and damage can result from perivascular extravasation, unintentional intra-arterial injection, and intraneuronal or perineuronal infiltration. Adverse reactions include burning, pain, thrombophlebitis, tissue necrosis, and gangrene. In some cases, surgical intervention, including fasciotomy, skin graft, and/or amputation have been required (see WARNINGS – Severe Tissue Injury, Including Gangrene).

Due to the risks of intravenous injection, the preferred route of administration of promethazine hydrochloride injection is deep intramuscular injection. Subcutaneous injection is contraindicated. See DOSAGE AND ADMINISTRATION for important notes on administration.

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DESCRIPTION

Promethazine hydrochloride injection, USP is a sterile, pyrogen-free solution for deep intramuscular or intravenous administration. Promethazine hydrochloride (10*H*-Phenothiazine-10-ethanamine,*N,N*, α -trimethyl-, monohydrochloride, (\pm)-) is a racemic compound and has the following structural formula:



Each mL contains promethazine hydrochloride, either 25 mg or 50 mg, edetate disodium 0.1 mg, calcium chloride 0.04 mg, sodium metabisulfite 0.25 mg and phenol 5 mg in Water for Injection. pH 4.0 to 5.5; buffered with acetic acid-sodium acetate.

Promethazine hydrochloride injection is a clear, colorless solution. The product is light sensitive. It should be inspected before use and discarded if either color or particulate is observed.

CLINICAL PHARMACOLOGY

Promethazine hydrochloride is a phenothiazine derivative which possesses antihistaminic, sedative, anti-motion-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 result in its relative lack (1/10 that of chlorpromazine) of dopamine antagonist properties. 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 is metabolized in the liver, with the sulfoxides of promethazine and N-desmethylpromethazine 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 AND USAGE

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.

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CONTRAINDICATIONS

Children less than 2 years of age

Promethazine hydrochloride injection is contraindicated for use in pediatric patients less than two years of age due to the risk of respiratory depression (see WARNINGS – Respiratory Depression).

Comatose state

Promethazine hydrochloride injection is contraindicated in comatose states.

Intra-arterial injection

Under no circumstances should promethazine hydrochloride injection be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene (see **WARNINGS—Severe Tissue Injury, Including Gangrene**).

Subcutaneous injection

Promethazine hydrochloride injection should not be given by the subcutaneous route because evidence of chemical irritation has been noted, and necrotic lesions have resulted following subcutaneous injection. The preferred parenteral route of administration is by deep intramuscular injection.

Idiosyncratic reaction or hypersensitivity

Promethazine hydrochloride injection is contraindicated in patients who have demonstrated an idiosyncratic reaction or hypersensitivity to promethazine or other phenothiazines.

WARNINGS

Respiratory Depression

Pediatrics

Promethazine hydrochloride injection should not be used in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression. Post-marketing cases of respiratory depression, including fatalities, have been reported with use of promethazine in pediatric patients less than 2 years of age. A wide range of weight-based doses of promethazine hydrochloride injection have resulted in respiratory depression in these patients.

Caution should be exercised when administering promethazine hydrochloride injection to pediatric patients 2 years of age and older. It is recommended that the lowest effective dose of promethazine hydrochloride injection be used in pediatric patients 2 years of age and older. Avoid concomitant administration of other drugs with respiratory depressant effects because of an association with respiratory depression, and sometimes death, in pediatric patients.

Other

Because of the risk of potentially fatal respiratory depression, use of promethazine hydrochloride injection in patients with compromised respiratory function or patients at risk for respiratory failure (e.g. COPD, sleep apnea) should be avoided.

Severe Tissue Injury, Including Gangrene

Promethazine hydrochloride injection can cause severe chemical irritation and damage to tissues regardless of the route of administration. Irritation and damage

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WARNINGS ¶

WARNING: PROMETHAZINE HYDROCHLORIDE INJECTION 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 PROMETHAZINE HYDROCHLORIDE INJECTION IN PEDIATRIC PATIENTS LESS THAN 2 YEARS OF AGE. A WIDE RANGE OF WEIGHT-BASED DOSES OF PROMETHAZINE HYDROCHLORIDE INJECTION HAVE RESULTED IN RESPIRATORY DEPRESSION IN THESE PATIENTS. ¶ CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PROMETHAZINE HYDROCHLORIDE INJECTION TO PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER. IT IS RECOMMENDED THAT THE LOWEST EFFECTIVE DOSE OF PROMETHAZINE HYDROCHLORIDE INJECTION BE USED IN PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER AND CONCOMITANT ADMINISTRATION OF OTHER DRUGS WITH RESPIRATORY DEPRESSANT EFFECTS BE AVOIDED.¶

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can result from perivascular extravasation, unintentional intra-arterial injection, and intraneuronal or perineuronal infiltration. Adverse event reports include burning, pain, erythema, swelling, sensory loss, palsies, paralysis, severe spasm of distal vessels, thrombophlebitis, venous thrombosis, phlebitis, abscesses, tissue necrosis, and gangrene. In some cases, surgical intervention, including fasciotomy, skin graft, and/or amputation have been required.

Because of the risks of intravenous injection, the preferred route of administration of promethazine hydrochloride injection is deep intramuscular injection (see DOSAGE AND ADMINISTRATION). Subcutaneous injection is contraindicated. 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 unintentional intra-arterial injection as pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances. Aspiration of dark blood does not preclude intra-arterial needle placement because blood is discolored upon contact with promethazine hydrochloride injection. Use of syringes with rigid plungers or of small-bore needles might obscure typical arterial backflow if this is relied upon alone.

In the event that a patient complains of pain during intravenous injection of promethazine hydrochloride injection, the injection should be stopped immediately to evaluate for possible arterial injection or perivascular extravasation.

There is no proven successful management of unintentional intra-arterial injection or perivascular extravasation after it occurs. Sympathetic block and heparinization have been employed during the acute management of unintentional intraarterial injection, because of the results of animal experiments with other known arteriolar irritants.

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CNS Depression

Promethazine hydrochloride injection 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, 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 hydrochloride (see **PRECAUTIONS—Information for Patients** and **Drug Interactions**).

Deleted: 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. ¶

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.

Deleted: Respiratory Depression ¶
Promethazine hydrochloride 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. ¶

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 hydrochloride 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 hydrochloride 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 hydrochloride, 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 hydrochloride should be carefully considered.

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.

Visual Inspection

This product is light sensitive and should be inspected before use and discarded if either color or particulate is observed.

Cholestatic Jaundice

Administration of promethazine has been associated with reported cholestatic jaundice.

PRECAUTIONS

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Use in Pediatric Patients ¶
PROMETHAZINE HYDROCHLORIDE INJECTION IS CONTRAINDICATED FOR USE IN PEDIATRIC PATIENTS LESS THAN TWO YEARS OF AGE. ¶ CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PROMETHAZINE HYDROCHLORIDE INJECTION 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 NOT FIRMLY WEIGHT-RELATED, WHICH MIGHT OTHERWISE PERMIT SAFE ADMINISTRATION OF INDIVIDUALIZED DOSING. 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 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 ... [1]

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Deleted: Other Considerations ¶
Sedative drugs or CNS depressants should be avoided in patients with a history of sleep apnea.

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

Patients should be advised of the risk of respiratory depression, including potentially fatal respiratory depression in children less than 2 years of age (see **WARNINGS – Respiratory Depression**).

Patients should be advised of the risk of severe tissue injury, including gangrene (see **WARNINGS – Severe Tissue Injury, Including Gangrene**). Patients should be advised to immediately report persistent or worsening pain or burning at the injection site.

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. Pediatric patients should be supervised to avoid potential harm in bike riding or in other hazardous activities. The concomitant use of alcohol, sedative/hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tricyclic antidepressants, and tranquilizers may enhance impairment (see **WARNINGS—CNS Depression** and **PRECAUTIONS—Drug Interactions**).

Patients should be advised to report any involuntary muscle movements (see **ADVERSE REACTIONS – Paradoxical Reactions**).

Patients should be advised to avoid prolonged exposure to the sun (see **ADVERSE REACTIONS – Dermatologic**).

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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, tricyclic antidepressants, and tranquilizers; therefore, such agents should be avoided or administered in reduced dosage to patients receiving promethazine hydrochloride. When given concomitantly with promethazine hydrochloride injection, 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 hydrochloride injection 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.

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Epinephrine

Because of the potential for promethazine hydrochloride to reverse epinephrine's

vasopressor effect, epinephrine should NOT be used to treat hypotension associated with promethazine hydrochloride injection overdose.

Anticholinergics

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

Monoamine Oxidase (MAO) Inhibitors

Drug interactions, including an increased incidence of extrapyramidal effects, have been reported when some MAO Inhibitors and phenothiazines are used concomitantly. This possibility should be considered with promethazine hydrochloride injection.

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Drug/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 blood glucose has been reported in patients receiving promethazine hydrochloride.

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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 *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 (approximately 2.1 and 4.2 times the maximum recommended human daily dose) of 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 administered to a pregnant woman within two weeks of delivery may inhibit platelet aggregation in the newborn.

Labor and Delivery

Promethazine hydrochloride injection may be used alone or as an adjunct to narcotic analgesics during labor (see **DOSAGE AND ADMINISTRATION**). Limited data suggest that use of promethazine hydrochloride injection 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 **Pregnancy—Nonteratogenic Effects.**)

Nursing Mothers

It is not known whether promethazine hydrochloride injection 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 injection, 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 injection is contraindicated for use in pediatric patients less than 2 years of age, because of the potential for fatal respiratory depression.

Promethazine hydrochloride injection should be used with caution in pediatric patients 2 years of age and older (see **WARNINGS—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, in pediatric patients may cause sudden death (see **OVERDOSAGE**).
Hallucinations and convulsions have occurred with therapeutic doses and overdoses of promethazine hydrochloride injection 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 hydrochloride injection.

Geriatric Use (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.

ADVERSE REACTIONS

Respiratory Depression

Promethazine hydrochloride injection is contraindicated in pediatric patients less than 2 years of age, because of the potential for fatal respiratory depression. Promethazine hydrochloride injection should be used with caution in pediatric patients 2 years of age and older (see **WARNINGS—Respiratory Depression**).

Severe Tissue Injury, including Gangrene

Promethazine hydrochloride injection can cause severe chemical irritation and damage to tissues regardless of the route of administration. Irritation and damage can result from perivascular extravasation, unintentional intra-arterial injection and intraneuronal or perineuronal infiltration. Adverse reactions include burning, pain, erythema, swelling,

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sensory loss, palsies, paralysis, severe spasm of distal vessels, thrombophlebitis, venous thrombosis, phlebitis, abscesses, tissue necrosis, and gangrene. In some cases, surgical intervention, including fasciotomy, skin graft, and/or amputation have been required (see **WARNINGS – Severe Tissue Injury, Including Gangrene; and DOSAGE AND ADMINISTRATION**).

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 hydrochloride injection. Consideration should be given to the discontinuation of promethazine hydrochloride injection 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 overdose 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 pediatric patients and geriatric patients. Convulsions may rarely occur. A paradoxical-type reaction has been reported in pediatric patients receiving single doses of 75 mg to 125 mg orally, characterized by hyperexcitability and nightmares.

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Deleted: Administration of promethazine hydrochloride injection has resulted in nerve damage ranging from temporary sensory loss to palsies and paralysis. Injection into or near a nerve may result in permanent tissue damage. Subcutaneous injection has resulted in tissue necrosis. Injection site reactions including burning, erythema, pain, and edema have been reported. Administration of promethazine hydrochloride injection has resulted in abscesses and/or tissue necrosis and gangrene, regardless of the route of administration. In some cases, surgical intervention (including fasciotomy, skin graft, and/or amputation) may be required (see **CONTRAINDICATIONS, WARNINGS—Injection Site Reactions, and DOSAGE AND ADMINISTRATION**).

Atropine-like signs and symptoms—dry mouth; fixed, dilated pupils; flushing; etc., 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. 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 norepinephrine 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.

DOSAGE AND ADMINISTRATION

Important Notes on Administration

Promethazine hydrochloride injection can cause severe chemical irritation and damage to tissues regardless of the route of administration. Irritation and damage can result from perivascular extravasation, unintentional intra-arterial injection, and intraneuronal or perineuronal infiltration (see WARNINGS – Severe Tissue Injury, Including Gangrene).

- The preferred parenteral route of administration for promethazine hydrochloride injection is by deep intramuscular injection.
- Under no circumstances should promethazine hydrochloride injection be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene (see WARNINGS – Severe Tissue Injury, Including Gangrene).
- Subcutaneous injection is contraindicated as it may result in tissue necrosis.
- When administered intravenously, promethazine hydrochloride injection should be given in a concentration no greater than 25 mg per mL and 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.
- In the event that a patient complains of pain during intravenous injection of promethazine hydrochloride injection, the injection should be stopped immediately to evaluate for possible arterial injection or perivascular extravasation.

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

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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.

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 dosage of analgesics and barbiturates should be reduced accordingly (see PRECAUTIONS – Drug Interactions).

Antiemetics should not be used in vomiting of unknown etiology in children and adolescents (see PRECAUTIONS – Pediatric Use).

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 (see PRECAUTIONS – Drug Interactions).

Promethazine hydrochloride is contraindicated for use in pediatric patients less than two years of age.

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 with an appropriately reduced dose of any desired narcotic (see PRECAUTIONS – Drug Interactions). 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.

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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. ¶

UNINTENTIONAL INTRA-ARTERIAL INJECTION CAN RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (see CONTRAINDICATIONS, WARNINGS—Injection Site Reactions). SUBCUTANEOUS INJECTION IS CONTRAINDICATED, AS IT MAY RESULT IN TISSUE NECROSIS (see CONTRAINDICATIONS, WARNINGS—Injection Site Reactions, and ADVERSE REACTIONS). ¶

Injection into or near a nerve may result in permanent tissue damage (see **ADVERSE REACTIONS**). ¶

When used intravenously, promethazine hydrochloride injection should be given in a 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.

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Pediatric Patients

Promethazine hydrochloride injection is contraindicated for use in pediatric patients less than 2 years of age (see WARNINGS—Respiratory Depression). Caution should be exercised when administering promethazine hydrochloride to pediatric patients 2 years of age or older. It is recommended that the lowest effective dose of promethazine hydrochloride be used in pediatric patients 2 years of age and older and concomitant administration of other drugs with respiratory depressant effects be avoided (see WARNINGS—Respiratory Depression).

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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 1.1 mg per kg of body weight in combination with an appropriately reduced dose of narcotic or barbiturate and the appropriate dose of an atropine-like drug (see PRECAUTIONS – Drug Interactions). Antiemetics should not be used in vomiting of unknown etiology in pediatric patients.

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HOW SUPPLIED

Promethazine hydrochloride injection, USP is available as follows:

NDC Number	Strength	Package
0703-2191-04	25 mg/mL	1 mL fill in a 2 mL vial 25 vial per shelf tray
0703-2201-04	50 mg/mL	1 mL fill in a 2 mL vial 25 vial per shelf tray

Store at 20-25°C (68°–77°F). [See USP Controlled Room Temperature]

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Protect from light. Keep covered in carton until time of use.

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Do not use if solution has developed color or contains a precipitate.

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Issued: September 2005

sicor™
SICOR Pharmaceuticals, Inc.
Irvine, CA 92618

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

ANDA-40454

ORIG-1

TEVA
PARENTERAL
MEDICINES INC

PROMETHAZINE
HYDROCHLORIDE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GARY J BUEHLER

09/16/2009