Promethazine: Drug information

(For additional information see "Promethazine: Patient drug information" and see "Promethazine: Pediatric drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

ALERT: US Boxed Warning

Respiratory depression - Pediatrics:

Promethazine should not be used in pediatric patients younger than 2 years because of the potential for fatal respiratory depression.

Postmarketing cases of respiratory depression, including fatalities, have been reported with the use of promethazine in pediatric patients younger than 2 years. A wide range of weight-based doses of promethazine have resulted in respiratory depression in these patients.

Exercise caution when administering promethazine to pediatric patients 2 years and older. It is recommended that the lowest effective dose of promethazine be used in pediatric patients 2 years and older and that coadministration with other drugs with respiratory-depressant effects be avoided.

Severe tissue injury, including gangrene (injection):

Promethazine 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.

Due to the risks of intravenous (IV) injection, the preferred route of administration of promethazine is deep intramuscular (IM) injection. Subcutaneous injection is contraindicated.

Brand Names: US

Phenadoz [DSC]; Phenergan; Promethegan

Pharmacologic Category

Antiemetic; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation; Phenothiazine Derivative

Dosing: Adult

Note: ISMP discourages the use of injectable promethazine (any route) because of the risk of severe tissue damage (ISMP 2018).

Allergic conditions, treatment:

Oral, rectal: 25 mg at bedtime **or** 12.5 mg before meals and at bedtime (usual range: 6.25 to 12.5 mg 3 times daily)

IM, IV: 25 mg, may repeat in 2 hours when necessary; switch to oral route as soon as feasible

Motion sickness: Oral, rectal: Initial: 25 mg 30 to 60 minutes before departure; repeat 8 to 12 hours later as needed; maintenance: 25 mg twice daily.

Nausea and vomiting: Oral, IM, IV, rectal: 12.5 to 25 mg every 4 to 6 hours, as needed

Nausea and vomiting of pregnancy (off-label use): Oral, IM, IV, rectal: 12.5 to 25 mg every 4 to 6 hours, as needed (ACOG 189 2018)

Obstetrics (labor), adjunct to analgesia: IM, IV: Early labor: 50 mg; Established labor: 25 to 75 mg in combination with analgesic at reduced dosage; may repeat every 4 hours for up to 2 additional doses (maximum: 100 mg/day while in labor)

Surgical analgesia/hypnotic; pre-/postoperative adjunct: IM, IV: 25 to 50 mg in combination with analgesic or hypnotic (at reduced dosage)

Sedation: Oral, IM, IV, rectal: 25 to 50 mg/dose

Dosage adjustment for concomitant therapy: Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for

more information.

Dosing: Renal Impairment: Adult

There are no dosage adjustments provided in the manufacturer's labeling.

Dosing: Hepatic Impairment: Adult

There are no dosage adjustments provided in the manufacturer's labeling; use with caution (cholestatic jaundice has been reported with use).

Dosing: Pediatric

(For additional information see "Promethazine: Pediatric drug information")

Note: Use with extreme caution and utilize the lowest effective dose to reduce the risk of adverse effects with all routes of administration. Use has generally been replaced by agents that are more effective with fewer adverse events. Due to risk of severe tissue injury, IV and IM administration is generally avoided.

Nausea and vomiting:

Note: Promethazine has been used as an antiemetic for various presenting conditions (eg, postoperative nausea/vomiting, chemotherapy-induced nausea/vomiting, cyclic vomiting syndrome, migraine). In most clinical situations, routine use has been replaced by alternate agents from other therapeutic classes; however, promethazine may be necessary in refractory situations or as rescue therapy; may consider concomitant diphenhydramine to decrease risk of dystonic adverse effects (ASER/SAA [Gan 2020]; Flank 2015; Kovacic 2018; Sheridan 2018).

Children ≥2 years and Adolescents: Oral, IM, IV, rectal: Usual range: 0.25 to 0.5 mg/kg/dose every 4 to 6 hours as needed; doses up to 1.1 mg/kg/dose may be necessary in some patients; do not exceed usual adult dose of 6.25 to 25 mg/dose (ASER/SAA [Gan 2020]; Sheridan 2014; Smith 1974; Wyllie 2016; manufacturer's labeling).

Preprocedure sedation, adjunct: Children ≥2 years and Adolescents: Oral, IM, IV: 0.5 to 1.1 mg/kg once 30 minutes prior to procedure as part of an appropriate combination regimen; maximum dose: 12.5 to 25 mg/dose; manufacturer recommends in combination with a reduced dose of opioid or barbiturate and an appropriate dosage of an atropine-like drug if appropriate; however, other combination regimens have been described (Auden 2000; Bui 2002; Fallah 2014; Mozafar 2018; Petrack 1996; Schutzman 1996; manufacturer's labeling).

Dosage adjustment for concomitant therapy: Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information.

Dosing: Renal Impairment: Pediatric

Children ≥2 years and Adolescents: There are no dosage adjustments provided in the manufacturer's labeling.

Dosing: Hepatic Impairment: Pediatric

Children ≥ 2 years and Adolescents: The manufacturer recommends to avoid use in pediatric patients with signs and symptoms of hepatic disease (extrapyramidal symptoms caused by promethazine may be confused with CNS signs of hepatic disease).

Dosing: Geriatric

Avoid use (Beers Criteria [AGS 2019]).

Dosage Forms: US

Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Solution, Injection, as hydrochloride:

Phenergan: 50 mg/mL (1 mL) [contains edetate disodium, phenol, sodium metabisulfite]

Phenergan: 25 mg/mL (1 mL) [pyrogen free; contains edetate disodium, phenol, sodium metabisulfite]

Generic: 25 mg/mL (1 mL); 50 mg/mL (1 mL)

Solution, Oral, as hydrochloride:

Generic: 6.25 mg/5 mL (118 mL [DSC], 473 mL)

Suppository, Rectal, as hydrochloride:

Phenadoz: 12.5 mg (12 ea [DSC]); 25 mg (12 ea [DSC])

Phenergan: 12.5 mg (12 ea [DSC]); 25 mg (12 ea [DSC]); 50 mg (12 ea [DSC])

Promethegan: 12.5 mg (1 ea, 12 ea); 25 mg (12 ea, 1000 ea [DSC]); 50 mg (1 ea, 12 ea)

Generic: 12.5 mg (1 ea, 12 ea); 25 mg (1 ea, 12 ea); 50 mg (12 ea [DSC])

Syrup, Oral, as hydrochloride:

Generic: 6.25 mg/5 mL (118 mL [DSC], 473 mL)

Tablet, Oral, as hydrochloride:

Generic: 12.5 mg, 25 mg, 50 mg

Generic Equivalent Available: US

Yes

Dosage Forms: Canada

Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Solution, Injection, as hydrochloride:

Generic: 25 mg/mL ([DSC])

Administration: Adult

Oral: Administer with food, water, or milk to decrease GI distress. Measure and administer prescribed dose of oral solution using dosing syringe, dosing spoon, or dosing cup.

Parenteral: Not for SubQ administration; promethazine is a chemical irritant which may produce necrosis. **Note:** ISMP discourages the use of injectable promethazine (any route) because of the risk of severe tissue damage (ISMP 2018).

IM: Preferred route of parenteral administration; administer as a deep IM injection

IV: IV use should be avoided when possible since severe tissue damage has occurred with IV administration; in selected patients, promethazine has been diluted and infused at a maximum rate of 25 mg/minute. To minimize phlebitis, consider administering over 10 to 15 minutes, limiting initial dose to $^1/_4$ or $^1/_2$ the usual dose (eg, in adults 6.25 to 12.5 mg), further diluting the 25 mg/mL strength in 10 to 20 mL NS, and administering through a large bore vein (not hand or wrist) or via a running IV line at port farthest from patient's vein (Reynolds 2014).

Vesicant; ensure proper needle or catheter placement prior to and during infusion; avoid extravasation. Discontinue immediately if burning or pain occurs with

administration; evaluate for inadvertent arterial injection or extravasation.

Extravasation management: If extravasation occurs, stop infusion immediately and disconnect (leave cannula/needle in place); gently aspirate extravasated solution (do **NOT** flush the line); remove needle/cannula; elevate extremity. Information conflicts regarding the use of dry warm or dry cold compresses (Hurst 2004; Reynolds 2014).

Administration: Pediatric

Oral: Measure and administer prescribed dose of oral solution using dosing syringe, dosing spoon, or dosing cup.

Parenteral: **Not for SubQ** administration; promethazine is a chemical irritant which may produce necrosis; ISMP discourages use of injectable promethazine (any route) (ISMP 2018).

IM: Administer as a deep IM injection.

IV: IV use should be avoided when possible since severe tissue damage has occurred with IV administration. If used, promethazine should be administered diluted (eg, minibag or the 25 mg/mL preparation in at least 10 to 20 mL NS) and infused over 10 to 15 minutes or at a rate not to exceed 25 mg/minute; administer through a large bore vein (not hand or wrist) or via a running IV line at port farthest from patient's vein to reduce risk of phlebitis (ISMP 2006; Reynolds 2014).

Vesicant; ensure proper needle or catheter placement prior to and during infusion; avoid extravasation. Discontinue immediately if burning or pain occurs with administration; evaluate for inadvertent arterial injection or extravasation. If extravasation occurs, stop infusion immediately and disconnect (leave cannula/needle in place); gently aspirate extravasated solution (do **NOT** flush the line); remove needle/cannula; elevate extremity. Information varies regarding the use of dry warm **or** dry cold compresses (Hurst 2004; Reynolds 2014).

Use: Labeled Indications

Allergic conditions, treatment: Perennial and seasonal allergic rhinitis; vasomotor rhinitis; allergic conjunctivitis due to inhalant allergens and foods; mild, uncomplicated allergic skin manifestations of urticaria and angioedema; amelioration of allergic reactions to blood or plasma; dermographism; anaphylactic reactions, as adjunctive therapy to epinephrine and other standard measures, after the acute manifestations have been controlled

Nausea and vomiting: Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery; antiemetic therapy in postoperative patients

Motion sickness: Active and prophylactic treatment of motion sickness

Surgical analgesia/hypnotic; pre-/postoperative adjunct: Adjunctive therapy with analgesics and/or anesthesia

Sedation: Preoperative, postoperative, and obstetric sedation; for sedation, relief of apprehension, and production of light sleep from which the patient can be easily aroused

Use: Off-Label: Adult

Nausea and vomiting of pregnancy

Medication Safety Issues

Sound-alike/look-alike issues:

Promethazine may be confused with chlorproMAZINE, predniSONE

Phenergan may be confused with PHENobarbital, Phrenilin, Theragran

High alert medication:

The Institute for Safe Medication Practices (ISMP) includes this medication (injectable formulation) among its list of drugs that have a heightened risk of causing significant patient harm when used. ISMP strongly discourages use of injectable promethazine (any route) and suggests facilities remove from all areas (including pharmacy) and not allow practitioners to order (ISMP 2018).

Geriatric patients: High-risk medication:

Beers Criteria: Promethazine, a first-generation antihistamine, is identified in the Beers Criteria as a potentially inappropriate medication to be avoided in patients 65 years and older (independent of diagnosis or condition) due to its potent anticholinergic properties resulting in increased risk of confusion, dry mouth, constipation, and other anticholinergic effects or toxicity; use should also be avoided due to reduced clearance with advanced age and tolerance associated with use as a hypnotic (Beers Criteria [AGS 2019]).

Pharmacy Quality Alliance (PQA): Promethazine, as a single agent or as part of a combination, is identified as a high-risk medication in patients 65 years and older on the PQA's Use of High-Risk Medications in the Elderly (HRM) performance measure, a

safety measure used by the Centers for Medicare and Medicaid Services (CMS) for Medicare plans (PQA 2017).

Pediatric patients: High-risk medication:

KIDs List: Dopamine antagonists, when used in pediatric patients <18 years of age, are identified on the Key Potentially Inappropriate Drugs in Pediatrics (KIDs) list; use should be avoided in infants and used with caution in children and adolescents due to risk of acute dystonia (dyskinesia), and with intravenous administration an increased risk of respiratory depression, extravasation, and death (strong recommendation; moderate quality of evidence) (PPA [Meyers 2020]).

International issues:

Sominex: Brand name for promethazine in Great Britain, but also is a brand name for diphenhydrAMINE in the US

Adverse Reactions

The following adverse drug reactions and incidences are derived from product labeling unless otherwise specified.

Frequency not defined.

Cardiovascular: Bradycardia, decreased blood pressure, increased blood pressure, local thrombophlebitis (injection), localized phlebitis (injection), peripheral vasospasm (injection), tachycardia, venous thrombosis (injection)

Central nervous system: Abnormal sensory symptoms (injection), agitation, catatonia, confusion, delirium, disorientation, dizziness, drowsiness, euphoria, excitement, extrapyramidal reaction, fatigue, hallucination, hyperexcitability, hysteria, insomnia, lassitude, movement disorder, paralysis (injection), nervousness, neuroleptic malignant syndrome, nightmares, sedated state, seizure

Dermatologic: Dermatitis, gangrene of skin and/or other subcutaneous tissues (injection), skin photosensitivity, urticaria

Gastrointestinal: Nausea, vomiting, xerostomia

Hematologic & oncologic: Agranulocytosis, immune thrombocytopenia, leukopenia, thrombocytopenia

Hepatic: Cholestatic jaundice, jaundice

Hypersensitivity: Angioedema

Local: Abscess at injection site, burning sensation at injection site, erythema at injection site, local tissue necrosis (injection), pain at injection site, swelling at injection site

Neuromuscular & skeletal: Tremor

Ophthalmic: Blurred vision, diplopia

Otic: Tinnitus

Respiratory: Apnea, asthma, nasal congestion

<1%, postmarketing, and/or case reports: Respiratory depression

Contraindications

Hypersensitivity or idiosyncratic reaction to promethazine, other phenothiazines, or any component of the formulation; coma; treatment of lower respiratory tract symptoms, including asthma; children <2 years of age; intra-arterial or subcutaneous administration

Warnings/Precautions

Concerns related to adverse effects:

• Altered cardiac conduction: May alter cardiac conduction (life-threatening arrhythmias have occurred with therapeutic doses of phenothiazines).

• Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, pyloroduodenal obstruction, urinary retention, bladder neck obstruction, BPH, xerostomia, or visual problems.

• CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks that require mental alertness (eg, operating machinery or driving).

• Extrapyramidal symptoms: May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia.

• Neuroleptic malignant syndrome (NMS): Use may be associated with NMS; monitor for mental status changes, fever, muscle rigidity and/or autonomic instability.

• Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

• Photosensitivity: May cause photosensitivity; avoid prolonged sun exposure.

• Serious tissue injury: **[US Boxed Warning]: Promethazine injection can cause severe tissue injury (including gangrene) regardless of the route of administration. Tissue irritation and damage may result from perivascular extravasation, unintentional intra-arterial administration, and intraneuronal or perineuronal infiltration. In addition to gangrene, adverse events reported include tissue necrosis, abscesses, burning, pain, erythema, edema, severe spasm of distal vessels, phlebitis, thrombophlebitis, venous thrombosis, sensory loss, paralysis, and palsies. Surgical intervention including fasciotomy, skin graft, and/or amputation have been necessary in some cases. The preferred route of administration is by deep intramuscular (IM) injection. Subcutaneous administration is contraindicated. Discontinue intravenous injection immediately with onset of burning and/or pain and evaluate for arterial injection or perivascular extravasation. Although there is no proven successful management of unintentional intra-arterial injection or perivascular extravasation, sympathetic block and heparinization have been used in the acute management of unintentional intra-arterial injection based on results from animal studies.** Vesicant; for IV administration (**not** the preferred route of administration), ensure proper needle or catheter placement prior to and during administration; avoid extravasation. ISMP discourages the use of injectable promethazine (any route) because of the risk of severe tissue damage (ISMP 2018).

• Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

• Bone marrow suppression: Use with caution in patients with bone marrow suppression; leukopenia and agranulocytosis have been reported.

• Cardiovascular disease: Use with caution in patients with cardiovascular disease.

• Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade.

• Hepatic impairment: Use with caution in patients with hepatic impairment; cholestatic jaundice has been reported with use. Avoid use in pediatric patients with signs and symptoms of hepatic disease (extrapyramidal symptoms caused by promethazine may be confused with CNS signs of hepatic disease).

• Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.

• Parkinson disease: Use with caution in patients with Parkinson disease; may have increased risk of tardive dyskinesia.

• Respiratory disease: Avoid use in patients with compromised respiratory function or in patients at risk for respiratory failure (eg, COPD, sleep apnea); may lead to potentially fatal respiratory depression.

• Seizures: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Special populations:

• Pediatric: **[US Boxed Warning]: Respiratory depression, including fatalities, have been reported in children <2 years of age. Use contraindicated in children <2 years. In children ≥2 years, use the lowest possible dose; other drugs with respiratory depressant effects should be avoided.** Antiemetics are not recommended for the treatment of uncomplicated vomiting in pediatric patients; limit use to prolonged vomiting of known etiology. Avoid use in children who may have Reye syndrome or hepatic disease as adverse reactions caused by promethazine may be confused with signs of primary disease.

Dosage form specific issues:

• Benzyl alcohol and derivatives: Some dosage forms may contain sodium benzoate/benzoic acid; benzoic acid (benzoate) is a metabolite of benzyl alcohol; large amounts of benzyl alcohol (≥99 mg/kg/day) have been associated with a potentially fatal toxicity ("gasping syndrome") in neonates; the "gasping syndrome" consists of metabolic acidosis, respiratory distress, gasping respirations, CNS dysfunction (including convulsions, intracranial hemorrhage), hypotension and cardiovascular

collapse (AAP 1997; CDC 1982); some data suggests that benzoate displaces bilirubin from protein binding sites (Ahlfors 2001); avoid or use dosage forms containing benzyl alcohol derivative with caution in neonates. See manufacturer's labeling.

• Ethanol: Oral solution contains 7% ethyl alcohol.

• Sodium metabisulfite: Injection may contain sodium metabisulfite; may cause allergic reaction.

Warnings: Additional Pediatric Considerations

Pediatric patients with dehydration are at increased risk for development of dystonic reactions from promethazine.

Metabolism/Transport Effects

Substrate of CYP2B6 (minor), CYP2D6 (minor); **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Acetylcholinesterase Inhibitors: May diminish the therapeutic effect of Anticholinergic Agents. Anticholinergic Agents may diminish the therapeutic effect of Acetylcholinesterase Inhibitors. *Risk C: Monitor therapy*

Aclidinium: May enhance the anticholinergic effect of Anticholinergic Agents. *Risk X: Avoid combination*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alizapride: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Amantadine: May enhance the anticholinergic effect of Anticholinergic Agents. *Risk C: Monitor therapy*

Aminolevulinic Acid (Systemic): Photosensitizing Agents may enhance the photosensitizing effect of Aminolevulinic Acid (Systemic). *Risk X: Avoid combination*

Aminolevulinic Acid (Topical): Photosensitizing Agents may enhance the photosensitizing effect of Aminolevulinic Acid (Topical). *Risk C: Monitor therapy*

Anticholinergic Agents: May enhance the adverse/toxic effect of other Anticholinergic Agents. *Risk C: Monitor therapy*

Azelastine (Nasal): May enhance the CNS depressant effect of CNS Depressants. *Risk X: Avoid combination*

Blonanserin: CNS Depressants may enhance the CNS depressant effect of Blonanserin. Management: Use caution if coadministering blonanserin and CNS depressants; dose reduction of the other CNS depressant may be required. Strong CNS depressants should not be coadministered with blonanserin. *Risk D: Consider therapy modification*

Botulinum Toxin-Containing Products: May enhance the anticholinergic effect of Anticholinergic Agents. *Risk C: Monitor therapy*

Brexanolone: CNS Depressants may enhance the CNS depressant effect of Brexanolone. *Risk C: Monitor therapy*

Brimonidine (Topical): May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Bromopride: May enhance the adverse/toxic effect of Promethazine. *Risk X: Avoid combination*

Bromperidol: May enhance the CNS depressant effect of CNS Depressants. *Risk X: Avoid combination*

Buprenorphine: CNS Depressants may enhance the CNS depressant effect of Buprenorphine. Management: Consider reduced doses of other CNS depressants, and avoiding such drugs in patients at high risk of buprenorphine overuse/self-injection. Initiate buprenorphine at lower doses in patients already receiving CNS depressants. *Risk D: Consider therapy modification*

Cannabidiol: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Cannabis: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Chloral Betaine: May enhance the adverse/toxic effect of Anticholinergic Agents. *Risk C: Monitor therapy*

Chlormethiazole: May enhance the CNS depressant effect of CNS Depressants. Management: Monitor closely for evidence of excessive CNS depression. The

chlormethiazole labeling states that an appropriately reduced dose should be used if such a combination must be used. *Risk D: Consider therapy modification*

Chlorphenesin Carbamate: May enhance the adverse/toxic effect of CNS Depressants. *Risk C: Monitor therapy*

Cimetropium: Anticholinergic Agents may enhance the anticholinergic effect of Cimetropium. *Risk X: Avoid combination*

CloZAPine: Anticholinergic Agents may enhance the constipating effect of CloZAPine. Management: Consider alternatives to this combination whenever possible. If combined, monitor closely for signs and symptoms of gastrointestinal hypomotility and consider prophylactic laxative treatment. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Dimethindene (Topical): May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Doxylamine: May enhance the CNS depressant effect of CNS Depressants. Management: The manufacturer of Diclegis (doxylamine/pyridoxine), intended for use in pregnancy, specifically states that use with other CNS depressants is not recommended. *Risk C: Monitor therapy*

Dronabinol: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Droperidol: May enhance the CNS depressant effect of CNS Depressants. Management: Consider dose reductions of droperidol or of other CNS agents (eg, opioids, barbiturates) with concomitant use. *Risk D: Consider therapy modification*

Eluxadoline: Anticholinergic Agents may enhance the constipating effect of Eluxadoline. *Risk X: Avoid combination*

EPINEPHrine (Nasal): Promethazine may diminish the vasoconstricting effect of EPINEPHrine (Nasal). *Risk C: Monitor therapy*

EPINEPHrine (Oral Inhalation): Promethazine may diminish the therapeutic effect of EPINEPHrine (Oral Inhalation). *Risk C: Monitor therapy*

Epinephrine (Racemic): Promethazine may diminish the vasoconstricting effect of Epinephrine (Racemic). Management: Monitor for diminished vasoconstrictive effects of

racemic epinephrine (e.g., diminished efficacy when used for gingival retraction). This interaction is likely of less concern in patients receiving epinephrine for other purposes (e.g., bronchodilation). *Risk C: Monitor therapy*

EPINEPHrine (Systemic): Promethazine may diminish the vasoconstricting effect of EPINEPHrine (Systemic). Management: Avoid epinephrine and consider norepinephrine or phenylephrine when treating hypotension due to promethazine overdose. Consider alternative vasocontrictors in patients treated with promethazine. This combination may be indicated in anaphylaxis treatment. *Risk D: Consider therapy modification*

Esketamine: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Flunitrazepam: CNS Depressants may enhance the CNS depressant effect of Flunitrazepam. Management: Reduce the dose of CNS depressants when combined with flunitrazepam and monitor patients for evidence of CNS depression (eg, sedation, respiratory depression). Use non-CNS depressant alternatives when available. *Risk D: Consider therapy modification*

Gastrointestinal Agents (Prokinetic): Anticholinergic Agents may diminish the therapeutic effect of Gastrointestinal Agents (Prokinetic). *Risk C: Monitor therapy*

Glucagon: Anticholinergic Agents may enhance the adverse/toxic effect of Glucagon. Specifically, the risk of gastrointestinal adverse effects may be increased. *Risk C: Monitor therapy*

Glycopyrrolate (Oral Inhalation): Anticholinergic Agents may enhance the anticholinergic effect of Glycopyrrolate (Oral Inhalation). *Risk X: Avoid combination*

Glycopyrronium (Topical): May enhance the anticholinergic effect of Anticholinergic Agents. *Risk X: Avoid combination*

Haloperidol: Promethazine may enhance the anticholinergic effect of Haloperidol. Promethazine may enhance the CNS depressant effect of Haloperidol. Promethazine may increase the serum concentration of Haloperidol. *Risk C: Monitor therapy*

HydrOXYzine: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Ipratropium (Oral Inhalation): May enhance the anticholinergic effect of Anticholinergic Agents. *Risk X: Avoid combination*

Itopride: Anticholinergic Agents may diminish the therapeutic effect of Itopride. *Risk C: Monitor therapy*

Kava Kava: May enhance the adverse/toxic effect of CNS Depressants. *Risk C: Monitor therapy*

Lemborexant: May enhance the CNS depressant effect of CNS Depressants. Management: Dosage adjustments of lemborexant and of concomitant CNS depressants may be necessary when administered together because of potentially additive CNS depressant effects. Close monitoring for CNS depressant effects is necessary. *Risk D: Consider therapy modification*

Levosulpiride: Anticholinergic Agents may diminish the therapeutic effect of Levosulpiride. *Risk X: Avoid combination*

Lisuride: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Lofexidine: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Magnesium Sulfate: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Methotrimeprazine: CNS Depressants may enhance the CNS depressant effect of Methotrimeprazine. Methotrimeprazine may enhance the CNS depressant effect of CNS Depressants. Management: Reduce the usual dose of CNS depressants by 50% if starting methotrimeprazine until the dose of methotrimeprazine is stable. Monitor patient closely for evidence of CNS depression. *Risk D: Consider therapy modification*

Metoclopramide: May enhance the adverse/toxic effect of Promethazine. *Risk X: Avoid combination*

MetyroSINE: May enhance the adverse/toxic effect of Promethazine. *Risk C: Monitor therapy*

Mianserin: May enhance the anticholinergic effect of Anticholinergic Agents. *Risk C: Monitor therapy*

Minocycline (Systemic): May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Mirabegron: Anticholinergic Agents may enhance the adverse/toxic effect of Mirabegron. *Risk C: Monitor therapy*

Nabilone: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Nitroglycerin: Anticholinergic Agents may decrease the absorption of Nitroglycerin. Specifically, anticholinergic agents may decrease the dissolution of sublingual nitroglycerin tablets, possibly impairing or slowing nitroglycerin absorption. *Risk C: Monitor therapy*

Opioid Agonists: CNS Depressants may enhance the CNS depressant effect of Opioid Agonists. Management: Avoid concomitant use of opioid agonists and benzodiazepines or other CNS depressants when possible. These agents should only be combined if alternative treatment options are inadequate. If combined, limit the dosages and duration of each drug. *Risk D: Consider therapy modification*

Orphenadrine: CNS Depressants may enhance the CNS depressant effect of Orphenadrine. *Risk X: Avoid combination*

Oxatomide: May enhance the anticholinergic effect of Anticholinergic Agents. *Risk X: Avoid combination*

Oxomemazine: May enhance the CNS depressant effect of CNS Depressants. *Risk X: Avoid combination*

Oxybate Salt Products: CNS Depressants may enhance the CNS depressant effect of Oxybate Salt Products. Management: Consider alternatives to this combination when possible. If combined, dose reduction or discontinuation of one or more CNS depressants (including the oxybate salt product) should be considered. Interrupt oxybate salt treatment during short-term opioid use *Risk D: Consider therapy modification*

OxyCODONE: CNS Depressants may enhance the CNS depressant effect of OxyCODONE. Management: Avoid concomitant use of oxycodone and benzodiazepines or other CNS depressants when possible. These agents should only be combined if alternative treatment options are inadequate. If combined, limit the dosages and duration of each drug. *Risk D: Consider therapy modification*

Paraldehyde: CNS Depressants may enhance the CNS depressant effect of Paraldehyde. *Risk X: Avoid combination*

Perampanel: May enhance the CNS depressant effect of CNS Depressants. Management: Patients taking perampanel with any other drug that has CNS depressant activities should avoid complex and high-risk activities, particularly those such as driving that require

alertness and coordination, until they have experience using the combination. *Risk D: Consider therapy modification*

Piribedil: CNS Depressants may enhance the CNS depressant effect of Piribedil. *Risk C: Monitor therapy*

Porfimer: Photosensitizing Agents may enhance the photosensitizing effect of Porfimer. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. Management: Patients on drugs with substantial anticholinergic effects should avoid using any solid oral dosage form of potassium chloride. *Risk X: Avoid combination*

Potassium Citrate: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Citrate. *Risk X: Avoid combination*

Pramipexole: CNS Depressants may enhance the sedative effect of Pramipexole. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergic Agents. These effects are specific to the GI tract. *Risk X: Avoid combination*

Ramosetron: Anticholinergic Agents may enhance the constipating effect of Ramosetron. *Risk C: Monitor therapy*

Revefenacin: Anticholinergic Agents may enhance the anticholinergic effect of Revefenacin. *Risk X: Avoid combination*

ROPINIRole: CNS Depressants may enhance the sedative effect of ROPINIRole. *Risk C: Monitor therapy*

Rotigotine: CNS Depressants may enhance the sedative effect of Rotigotine. *Risk C: Monitor therapy*

Rufinamide: May enhance the adverse/toxic effect of CNS Depressants. Specifically, sleepiness and dizziness may be enhanced. *Risk C: Monitor therapy*

Secretin: Anticholinergic Agents may diminish the therapeutic effect of Secretin. Management: Avoid concomitant use of anticholinergic agents and secretin. Discontinue anticholinergic agents at least 5 half-lives prior to administration of secretin. *Risk D: Consider therapy modification*

Suvorexant: CNS Depressants may enhance the CNS depressant effect of Suvorexant. Management: Dose reduction of suvorexant and/or any other CNS depressant may be necessary. Use of suvorexant with alcohol is not recommended, and the use of suvorexant with any other drug to treat insomnia is not recommended. *Risk D: Consider therapy modification*

Tetrahydrocannabinol: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Tetrahydrocannabinol and Cannabidiol: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Thalidomide: CNS Depressants may enhance the CNS depressant effect of Thalidomide. *Risk X: Avoid combination*

Thiazide and Thiazide-Like Diuretics: Anticholinergic Agents may increase the serum concentration of Thiazide and Thiazide-Like Diuretics. *Risk C: Monitor therapy*

Tiotropium: Anticholinergic Agents may enhance the anticholinergic effect of Tiotropium. *Risk X: Avoid combination*

Topiramate: Anticholinergic Agents may enhance the adverse/toxic effect of Topiramate. *Risk C: Monitor therapy*

Trimeprazine: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Umeclidinium: May enhance the anticholinergic effect of Anticholinergic Agents. *Risk X: Avoid combination*

Verteporfin: Photosensitizing Agents may enhance the photosensitizing effect of Verteporfin. *Risk C: Monitor therapy*

Zolpidem: CNS Depressants may enhance the CNS depressant effect of Zolpidem. Management: Reduce the Intermezzo brand sublingual zolpidem adult dose to 1.75 mg for men who are also receiving other CNS depressants. No such dose change is recommended for women. Avoid use with other CNS depressants at bedtime; avoid use with alcohol. *Risk D: Consider therapy modification*

Reproductive Considerations

Following use of promethazine, hCG-based pregnancy tests may result in false-negatives or false-positives.

Pregnancy Risk Factor

C (show table)

Pregnancy Considerations

Promethazine crosses the placenta (Potts 1961). Platelet aggregation may be inhibited in newborns following maternal use of promethazine within 2 weeks of delivery.

Promethazine is indicated for use during labor for obstetric sedation and may be used alone or as an adjunct to opioid analgesics. Promethazine may be used as adjunctive therapy in the management of nausea and vomiting of pregnancy when the preferred agents do not provide initial symptom improvement or when symptoms persist despite other therapies (ACOG 189 2018). Although promethazine is approved for the treatment of allergic conditions (eg, allergic rhinitis, urticaria), other agents are preferred for use in pregnancy (BSACI [Powell 2015]; BSACI [Scadding 2017]; Zuberbier 2018).

Breast-Feeding Considerations

It is not known if promethazine is present in breast milk.

Drowsiness and irritability have been reported in breastfed infants exposed to other antihistamines (Ito 1993). Due to the potential for serious adverse reactions in the breastfed infant, the manufacturer recommends a decision be made to discontinue breastfeeding or to discontinue the drug, taking into account the importance of treatment to the mother. Single maternal doses of promethazine may be compatible with breastfeeding; repeated doses should be avoided (WHO 2002). In general, first generation antihistamines should be used with caution in breastfeeding women and breastfed infants should be monitored for irritability or drowsiness (Butler 2014; WHO 2002).

When treatment with an antihistamine is needed in breastfeeding women, second generation antihistamines are preferred (BSACI [Powell 2015]; Butler 2014; Zuberbier 2018).

Antihistamines may decrease maternal serum prolactin concentrations when administered prior to the establishment of lactation (Messinis 1985).

Dietary Considerations

Increase dietary intake of riboflavin.

Monitoring Parameters

Relief of symptoms, mental status, and CNS effects (including sedation, akathisia, delirium, extrapyramidal symptoms); signs and symptoms of tissue injury (burning or pain at injection site, phlebitis, edema) with IV administration

Mechanism of Action

Phenothiazine derivative; blocks postsynaptic mesolimbic dopaminergic receptors in the brain; exhibits a strong alpha-adrenergic blocking effect and depresses the release of hypothalamic and hypophyseal hormones; competes with histamine for the H_1-receptor; muscarinic-blocking effect may be responsible for antiemetic activity; reduces stimuli to the brainstem reticular system

Pharmacodynamics and Pharmacokinetics

Onset of action: Oral, IM: ~20 minutes; IV: ~5 minutes

Duration: Usually 4 to 6 hours (up to 12 hours)

Absorption: Oral: Rapid and complete; large first pass effect limits systemic bioavailability (Sharma 2003)

Distribution: V_d: 13.4 ± 3.6 L/kg (Brunton 2011)

Protein binding: 93% (Brunton 2011)

Metabolism: Hepatic; hydroxylation via CYP2D6 and N-demethylation via CYP2B6; significant first-pass effect (Sharma 2003)

Bioavailability: Oral: ~25% (Sharma 2003); Rectal: 21.7% to 23.4% (Brunton 2011)

Half-life elimination: IM: ~10 hours; IV: 9 to 16 hours; Suppositories, syrup: 16 to 19 hours (range: 4 to 34 hours) (Strenkoski-Nix 2000)

Time to maximum serum concentration (Brunton 2011): Oral (syrup): 2.8 ± 1.4 hours; Rectal: 8.2 ± 3.4 hours

Excretion: Urine, feces as inactive metabolites

Pricing: US

Solution (Phenergan Injection)

25 mg/mL (per mL): $4.04

50 mg/mL (per mL): $5.60

Solution (Promethazine HCl Injection)

25 mg/mL (per mL): $1.01 - $2.50

50 mg/mL (per mL): $2.22 - $4.62

Suppository (Promethazine HCl Rectal)

12.5 mg (per each): $17.71

25 mg (per each): $17.71

Suppository (Promethegan Rectal)

12.5 mg (per each): $17.71

25 mg (per each): $17.71

50 mg (per each): $35.77

Syrup (Promethazine HCl Oral)

6.25 mg/5 mL (per mL): $0.05 - $0.10

Tablets (Promethazine HCl Oral)

12.5 mg (per each): $0.49

25 mg (per each): $0.10 - $0.95

50 mg (per each): $0.42 - $0.78

Disclaimer: A representative AWP (Average Wholesale Price) price or price range is provided as reference price only. A range is provided when more than one manufacturer's AWP price is available and uses the low and high price reported by the manufacturers to determine the range. The pricing data should be used for benchmarking purposes only, and as such should not be used alone to set or adjudicate any prices for reimbursement or purchasing functions or considered to be an exact price for a single product and/or manufacturer. Medi-Span expressly disclaims all warranties of any kind or nature, whether express or implied, and assumes no liability with respect to accuracy of price or price range data published in its solutions. In no

event shall Medi-Span be liable for special, indirect, incidental, or consequential damages arising from use of price or price range data. Pricing data is updated monthly.

Brand Names: International

Allerfen (IT); Allergin (BD); Allersoothe (AU, NZ); Antiallersin (BG); Atcopromezine (EG); Atosil (DE); Avomine (MT, TR); Diphergan (PL); Duplamin (IT); Fargan (IT); Farganesse (IT); Fenazil (IT); Fenazine (AE, CY, IQ, IR, JO, KW, LY, OM, SA, SY, YE); Fenergan (AR, ES, PE, PT, PY, UY, VE); Hibechin (JP); Hiberna (JP); Himazin (KR); Histaloc (AE, BH, KW, QA, SA); Histazan (JO); Histazin (AE, BH, CY, IQ, IR, JO, KW, LY, OM, SA, SY, YE); Histin (BD); Lergigan (SE); Meta (TH); Montil (BD); Phenergan (AE, AT, AU, BB, BF, BJ, BM, BS, BZ, CH, CI, CY, DK, ET, FI, FR, GB, GH, GM, GN, GR, GY, IE, IN, IQ, IR, IS, JM, JO, KE, KW, LR, LU, LY, MA, ML, MR, MT, MU, MW, MY, NE, NG, NO, NZ, OM, PK, SA, SC, SD, SL, SN, SR, SY, TN, TR, TT, TZ, UG, YE, ZA, ZM, ZW); Phenerzin (PH); Pipolphen (HN, HU, UA); Profergan (BR); Progic (BD); Prome (ID); Promeright (LK); Promet (JO, PH); Prometal (LB); Prometazina (IT); Prometazina Cloridrato (IT); Prometin (BH, QA); Promezine (MY); Proneurin (DE); Protha (TW); Prothazin (CZ); Prothiazine (IL); Provita (LK); Proz (LK); Prromine (PH); Pyrethia (JP); Romergon (RO); Sandoz Fenezal (AU); Sylomet (PH); Xepagan (MY)

For country abbreviations used in Lexicomp (show table)

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