DBL™ Promethazine Hydrochloride Injection BP

1. NAME OF THE MEDICINE

Promethazine hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of the solution contains 25.0 mg promethazine hydrochloride, 0.10 mg disodium edetate, 1.30 microlitre glacial acetic acid, 27.2 mg sodium acetate and 1.32 mg sodium metabisulfite in water for injections.

Excipient(s) with known effect

Sodium metabisulfite

For the full list of excipients, see section **6.1 List of Excipients**.

3. PHARMACEUTICAL FORM

Solution for injection.

DBL™ Promethazine Hydrochloride Injection BP is a clear, colourless solution of pH 5.0 to 6.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

DBL™ Promethazine Hydrochloride Injection BP is indicated for the following conditions:

Treatment of allergic reactions such as:

- uncomplicated allergic conditions of the immediate type, e.g., pruritus, urticaria and angioedema, when oral therapy is impossible or contraindicated.

Treatment and prevention of vomiting including:

- motion sickness;
- drug induced nausea;
- prevention and control of nausea and vomiting associated with certain types of anaesthesia and surgery, such as procedures with a high incidence of post-operative vomiting (e.g., gynaecological surgery, strabismus or middle ear surgery, and electroconvulsive therapy); in patients with a past history of motion sickness or post-operative vomiting; and in patients in whom avoidance of vomiting is crucial (e.g., neurosurgery and eye surgery).

Promethazine has sedative effects and it is also used in:

- pre-operative, post-operative and obstetric (during labour) sedation.

4.2 Dose and Method of Administration

Dosage

Allergic conditions

Adults: 25 mg to 50 mg by deep intramuscular injection or slow intravenous injection; may be repeated within two hours if necessary. Maximum dose up to 150 mg daily.

Antiemetic

Antiemetics should not be used in vomiting of unknown etiology in children and adolescents (see section **4.4 Special Warnings and Precautions for Use**).

In established nausea or vomiting due to causes other than motion sickness:

Adults: 12.5 to 25 mg, by intramuscular or intravenous injection, every four hours as needed.

Children: 5 to 12 yrs old - 12.5 mg by intramuscular injection.

Sedative/hypnotic

Adults: 25 to 50 mg by intramuscular or intravenous injection.

Children: When oral route is not possible;

2 to 5 yrs old - 7.5 to 10 mg by intramuscular injection.

6 to 10 yrs old - 10 to 12.5 mg by intramuscular injection.

Pre-operative and post-operative sedation

Adults: 25 to 50 mg by intramuscular or intravenous injection, usually with pethidine and atropine.

Obstetric sedation

Early stages of labour: 50 mg, by intramuscular injection. Established labour: 25 to 75 mg, by intramuscular or intravenous injection, with an appropriately reduced dose of an opioid analgesic. May be repeated once or twice at four hourly intervals during the course of the labour, if necessary. Total dose should not exceed 100 mg in 24 hours.

Method of Administration

All routes of administration can cause damage to tissues (see sections **4.8 Contraindications** and **4.4 Special Warnings and Precautions for Use**).

Deep Intramuscular Injection is the preferred route of administration of DBL™ Promethazine Hydrochloride Injection BP.

Promethazine should only be administered intravenously if the benefits outweigh the risks in an individual patient. This may include emergency situations or situations where IM injections are contraindicated (see section **4.4 Special Warnings and Precautions for Use**). Extreme care must be taken to avoid extravasation or intra-arterial injection. Injections should be stopped immediately if a patient complains of pain during injection (see section **4.4 Special Warnings and Precautions for Use**).

If venous administration is required, a large vein should be used. Administration via a venous site in the hand or wrist should be avoided if possible due to an increased risk of tissue injury.

When given intravenously, DBL™ Promethazine Hydrochloride Injection BP 50 mg/2 mL should be diluted 1 in 10 with water for injections or preferably given through the tubing of a freely flowing IV infusion. It should be injected slowly at a rate of administration not greater than 25 mg/minute (i.e. 10 mL/minute of dilute solution).

Rapid intravenous infusion may cause a transient fall in blood pressure and may increase the risk of severe tissue injuries. Promethazine should not be given intra-arterially or subcutaneously (see section **4.8 Contraindications**).

4.3 Contraindications

Promethazine is contraindicated for use in paediatric patients less than two years of age because of the potential for fatal respiratory depression. Post marketing cases of respiratory depression including fatalities have been reported with the use of promethazine in paediatric patients less than two years of age. A wide range of weight-based doses of promethazine have resulted in respiratory depression in these patients (see section **4.4 Special Warnings and Precautions for Use**).

Promethazine is contraindicated in patients who have exhibited hypersensitivity to the drug or other phenothiazine derivatives.

Promethazine is also contraindicated in the following patients:

- Comatose;
- after administration of large doses of other CNS depressants (e.g., alcohol, general anaesthetics, opioid analgesics, tranquillisers, etc.).

Intra-arterially administration of DBL™ Promethazine Hydrochloride Injection BP is contraindicated due to the likelihood of severe arteriospasm and the possibility of resultant gangrene.

Subcutaneous administration of DBL™ Promethazine Hydrochloride Injection BP is contraindicated, as the solution is an irritant and may produce necrotic lesions.

4.4 Special Warnings and Precautions for Use

This product should not be used in children under 2 years of age due to the potential for fatal respiratory depression (see section **4.3 Contraindications**).

Antiemetics are not recommended for treatment of uncomplicated vomiting in paediatric patients, and their use should be limited to prolonged vomiting of known etiology.

As a result of its anticholinergic actions, promethazine should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, and bladder neck obstruction. It should also be used with caution in patients with bone marrow depression, jaundice, impaired liver function, epilepsy, asthmatic attack, or cardiovascular disorders.

Promethazine may mask the adverse effects of ototoxic medications, e.g., tinnitus, dizziness. Concurrent use of promethazine and other hypotension producing medications may produce additive hypotensive effects. Concurrent use of promethazine with other hepatotoxic medications may increase the potential for hepatotoxicity, and patients should be carefully monitored.

Promethazine's antiemetic action may mask the symptoms of acute appendicitis or overdose of other drugs.

QT interval prolongation has been reported with phenothiazines.

The concomitant administration of alcohol, sedative-hypnotics, general anaesthetics, opioids, tranquillisers or other CNS depressants may have an additive sedative effect. Patients should be warned accordingly.

DBL™ Promethazine Hydrochloride Injection BP contains sodium metabisulfite, which may cause allergic type reactions, including anaphylactic symptoms and life threatening or less severe asthmatic episodes, in certain susceptible people.

Intravenous Use:

Promethazine is highly caustic to the intima of blood vessels and surrounding tissues. Intravenous administration can cause severe tissue injury including gangrene, which may require surgical intervention including fasciotomy, skin graft, and/or amputation. Severe tissue injury may result from perivascular extravasation, unintentional intra-arterial injection, and intraneuronal or perineuronal infiltration. Prescribes should be aware of early sign of tissue injury including burning or pain at the injection site, phlebitis, swelling and blistering. Injections should be stopped immediately if any of these symptoms occur.

If venous administration is required, a large vein should be used. Administration via a venous site in the hand or wrist should be avoided if possible due to an increased risk of tissue injury.

Use in the elderly

No data available.

Paediatric use

Caution should be exercised when administering promethazine to paediatric patients two years of age or older, because of the potential for fatal respiratory depression, including central and obstructive apnoea and reduced arousal. Respiratory depression and apnoea, sometimes fatal, are associated with promethazine even if individualised weight-based dosing is used. It is recommended that the lowest effective dose of promethazine be used in paediatric patients 2 years of age and older and concomitant administration of other drugs with respiratory depressant effects be avoided.

Use of promethazine should be avoided in acutely ill or dehydrated children, since these patients have an increased susceptibility to dystonias. Use of the drug should also be avoided in children and adolescents with signs and symptoms which suggest Reye's syndrome, since the potential extrapyramidal effects produced by the drug may obscure the diagnosis of, or be confused with the CNS signs and symptoms of this condition or other hepatic diseases. Excessively large doses in children may cause hallucinations, convulsions and sudden death. Children may experience paradoxical excitation with promethazine.

Effects on laboratory tests

Promethazine may interfere with diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG, and may cause an increase in glucose tolerance. Promethazine may produce false negative results in skin tests using allergen extracts. It is recommended that antihistamines are discontinued at least 72 hours before testing begins.

4.5 Interactions with Other Medicines and Other Forms of Interactions

Anticholinergics: Anticholinergic effects may be potentiated when these medications are used concurrently with promethazine. Patients should be advised to report occurrence of gastrointestinal problems promptly, since paralytic ileus may occur with concurrent therapy.

Anticonvulsants: As promethazine may lower the convulsion threshold, dosage adjustment of anticonvulsant medication may be required.

Antihypertensive agents: Concurrent use of promethazine with beta blockers, especially propranolol, may result in increased plasma concentrations of each agent because of inhibition of metabolism. This may result in additive hypotensive effects, irreversible retinopathy, cardiac arrhythmias and tardive dyskinesia.

The neuronal uptake of guanethidine may be inhibited when used with promethazine, causing a decrease in the antihypertensive effect.

Bromocriptine: Increase serum prolactin concentrations, thereby interfering with the effects of bromocriptine. Dosage adjustments of bromocriptine may be necessary.

CNS depressants: Promethazine may potentiate the sedative action of other CNS depressants such as barbiturates, antihistamines, tranquillisers, opioids, general anaesthetics, or alcohol.

Levodopa: The antiparkinsonian effects of levodopa may be inhibited when used

concurrently with promethazine because of blockade of dopamine receptors in the brain.

Metrizamide: Concurrent use of intrathecal metrizamide with promethazine may lower the seizure threshold. Promethazine should be discontinued at least 48 hours before, and not resumed for at least 24 hours following myelography.

Monoamine oxidase (MAO) inhibitors: Concurrent use of MAO inhibitors with promethazine may prolong and intensify the anticholinergic and CNS depressant effects, and may increase the risk of hypotension and extrapyramidal reactions.

Phenothiazine derivatives: Concurrent use of other phenothiazine derivatives may increase the severity and frequency of extrapyramidal effects.

Quinidine: Concurrent use of promethazine with quinidine may result in additive cardiac effects.

Sympathomimetic agents: The alpha adrenoceptor agonist effects of adrenaline may be blocked when it is used concurrently with promethazine, possibly resulting in severe hypotension and tachycardia. The alpha adrenoceptor blocking activity of promethazine may also decrease the pressor response to ephedrine, metaraminol and methoxamine; decrease the stimulant effects of amphetamines; and antagonise the anorectic effect of the centrally acting appetite suppressants.

Tricyclic antidepressants: Concurrent use of tricyclic antidepressants may intensify the anticholinergic effects and increase the risk of hypotension and extrapyramidal effects.

4.6 Fertility, Pregnancy and Lactation

Effects on fertility

No data available.

Use in pregnancy

When given in high doses during late pregnancy, phenothiazines have caused prolonged extrapyramidal disturbances in the child.

Use in lactation

The exact amount of promethazine excreted into breast milk is unknown, but amounts are usually small. Promethazine should be used with caution in nursing women. The infant should be observed for side effects, especially sedation.

4.7 Effects on Ability to Drive and Use Machines

Promethazine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a vehicle or operating machinery.

4.8 Adverse Effects (Undesirable Effects)

CNS: Sedation is the most prominent CNS effect of promethazine. Extrapyramidal reactions may occur with high doses and usually subside with dosage reduction. Other reported reactions include dizziness, lassitude, tinnitus, confusion, disorientation, incoordination, fatigue, blurred vision, euphoria, diplopia, nervousness, irritability, tremors, convulsions, oculogyric crises, excitation, catatonic-like states, and hysteria.

Cardiovascular: Tachycardia, bradycardia, faintness, dizziness, transient minor increases in blood pressure, and hypotension have been reported following the use of DBL™ Promethazine Hydrochloride Injection BP. Venous thrombosis at the injection site has been reported.

Gastrointestinal: Nausea and vomiting have been reported, usually in association with surgical procedures and combination drug therapy. Loss of appetite, epigastric distress, constipation and diarrhoea have also been reported.

Allergic: Urticaria, dermatitis, pruritus, asthma, photosensitivity, and angioneurotic oedema have been reported.

Other reported reactions: Leukopenia and agranulocytosis, usually when promethazine has been used in association with other known toxic agents; anaphylaxis, thrombocytopenic purpura; obstructive jaundice; tissue necrosis following subcutaneous injection; nasal stuffiness; and dry mouth.

4.9 Overdose

Symptoms

Symptoms of overdose range from mild depression of the CNS and cardiovascular system (drowsiness, bradycardia, tachycardia, and transient increases in blood pressure) to profound hypotension, respiratory depression, and unconsciousness. Paradoxical CNS stimulation (hallucinations, seizures, nightmares and trouble in sleeping) may be evident, especially in children and the elderly. Anticholinergic symptoms (severe dryness of mouth, nose or throat, flushing or redness of face, trouble in breathing), and extrapyramidal effects (muscle spasms, especially of the neck and back, restlessness, tic-like movements of head and face, trembling of hands) may occur.

Treatment

Treatment of promethazine overdosage is similar to that of other phenothiazine derivatives. Symptomatic supportive therapy is indicated and general physiologic measures such as maintenance of adequate ventilation should be instituted if necessary. Analeptics may cause convulsions and should not be used. Convulsions may be controlled with diazepam or barbiturates. Anticholinergic antiparkinsonism agents may be used to treat severe extrapyramidal reactions. Severe hypotension may respond to administration of noradrenaline or phenylephrine, but should not be treated with adrenaline because it may lower the blood pressure further.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of action

Promethazine is a phenothiazine derivative with potent antihistaminic and sedative-hypnotic effects. It also has antiemetic, antivertigo, anti-motion sickness, anticholinergic effects and local anaesthetic actions.

Antihistamines competitively and reversibly antagonise the effects of histamine at the H_1-receptor sites on effector cells which are responsible for vasodilatation, increased capillary permeability, flare and itch reactions in the skin, and to some extent for contraction of smooth muscle in the bronchi and gastrointestinal tract.

The precise mechanism of the CNS effects of promethazine is unknown. The sedative effects may involve antagonism at central histamine, serotonin and acetylcholine receptors, or central alpha adrenergic stimulation. However, paradoxical CNS stimulation may occur, especially in children, and at high doses may be attributable to antimuscarinic activity. The antiemetic, anti-motion sickness and antivertigo effects of promethazine are possibly a result of central anticholinergic actions on the vestibular apparatus and the integrative vomiting centre and medullary chemoreceptive trigger zone of the midbrain.

The anticholinergic (antimuscarinic) actions of promethazine provide a drying effect on the oral and nasal mucosa.

Clinical trials

No data available.

5.2 Pharmacokinetic Properties

Promethazine is well absorbed from parenteral sites and the onset of antihistaminic properties occurs about 20 minutes after intramuscular injection and 3 to 5 minutes after intravenous injection. It has a prolonged antihistamine action, which may persist for 12 hours or more. The duration of sedative effects may range from 2 to 8 hours depending on the dose and route of administration.

Promethazine is widely distributed within body tissues. Promethazine crosses the blood-brain barrier, and the placenta and is excreted in breast milk. It is metabolised by the liver and excreted slowly in the urine and faeces mainly as inactive promethazine sulphoxide and glucuronides; elimination half lives of 7 to 14 hours have been reported.

5.3 Preclinical Safety Data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Disodium edetate

Glacial acetic acid

Sodium acetate

Sodium metabisulfite

Water for injections

6.2 Incompatibilities

Solutions of promethazine hydrochloride are incompatible with alkaline substances, which precipitate the insoluble promethazine base. Promethazine has been reported to be incompatible with solutions containing the following compounds: aminophylline, benzylpenicillin salts, cefepime hydrochloride, cefotetan disodium, cephazolin, chloramphenicol sodium succinate, chloroquine phosphate, chlorothiazide sodium, dexamethasone sodium phosphate, dextran, dimenhydrinate, flucloxacillin sodium, foscarnet, frusemide, heparin sodium, hydrocortisone sodium succinate, ketorolac tromethamine, meglumine diatrizoate, meglumine iodipamide, methicillin sodium, methohexitone sodium, methotrexate sodium, morphine sulfate, nalbuphine hydrochloride (some formulations only), nitrofurantoin, penicillin G, pentobarbitone sodium, phenobarbitone sodium, phenytoin sodium, piperacillin, sodium bicarbonate, sodium diatrazoate, sodium iothalamate, sulphafurazole, thiopentone sodium.

6.3 Shelf Life

Refer to Outer Carton.

6.4 Special Precautions for Storage

Store below 25°C. Protect from light.

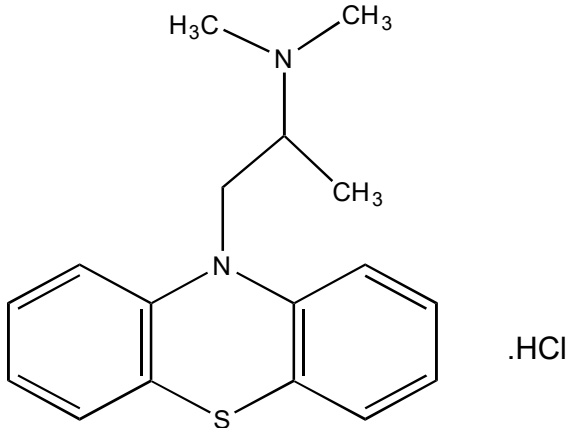
6.5 Nature and Contents of Container

DBL™ Promethazine Hydrochloride Injection BP is available as follows:

Strength	**Pack**
50 mg/2 mL	5 x 2 mL coloured glass ampoules

6.6 Physicochemical Properties

Chemical structure



Molecular formula: $C_{17}H_{20}N_2S.HCl$

Molecular weight: 320.9

CAS number

58-33-3

7. NAME AND ADDRESS OF PRODUCT OWNER

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PRO-SIN-1019/0
Date of last revision: October 2019