AUSTRALIAN PRODUCT INFORMATION – PHENERGAN® (PROMETHAZINE HYDROCHLORIDE) TABLET AND ELIXIR

1 NAME OF THE MEDICINE

Promethazine hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Phenergan Elixir contains promethazine hydrochloride 5 mg / 5 mL.

Excipients with known effect: maltitol solution, sodium benzoate, sodium sulfite, sodium metabisulfite.

Phenergan tablets contain 10 mg or 25 mg of promethazine hydrochloride.

Excipients with known effect: lactose monohydrate.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Elixir : **5 mg/5 mL**
Sugar free, alcohol free, orange flavoured, clear, bright, golden syrupy liquid.

Tablets : **10 mg**

Circular, film-coated biconvex tablets with bevelled edges, pale blue in colour, one face impressed 'PN' above '10', the reverse face plain.

25 mg

Circular, film-coated biconvex tablets with bevelled edges, pale blue in colour, one face impressed 'PN' above '25', the reverse face plain.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Allergies: Treatment of allergic conditions including some allergic reactions to drugs, urticaria and allergic contact dermatitis, and allergic reactions to insect bites and stings.

Upper respiratory tract: Relief of excessive secretion in the upper respiratory tract as a result of hayfever and allergic rhinitis.

Nausea and vomiting: Antiemetic for vomiting from various causes, including postoperative vomiting, irradiation sickness, drug induced nausea and motion sickness.

Sedation: For short term use under the advice of a doctor or pharmacist. Do not use for more than 7 to 10 consecutive days.

Other: Promethazine has sedative effects and can be used in the symptomatic management of measles and chicken pox.

Promethazine can be used as a preanaesthetic medication for the prevention and control of post operative vomiting.

4.2 DOSE AND METHOD OF ADMINISTRATION

This product must not be used in children under 2 years of age (see Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use). This product is not suitable for children aged 2 – 12 years unless on pharmacist or medical advice (see Section 4.4 Special warnings and precautions for use).

Dosage varies according to the condition being treated and the individual's response.

Tablets

The tablets are not recommended for children under 6 years of age.

Allergic disorder

Adults:	25 to 75 mg as a single dose at night, or 10 to 20 mg two to three times daily
Children:	6 – 12 years: 10 to 25 mg as a single dose at night, or 10 mg two to three times daily

Sedation

Adults:	25 to 75 mg as a single dose at night
Children:	6 – 12 years: 10 to 25 mg as a single dose at night

Travel sickness

Adults: 25 mg
Children: 6 – 12 years: 10 mg
To be taken the night before travel and repeated after 6 to 8 hours on the following day if required.

Nausea and vomiting

Adults: 25 mg every 4 to 6 hours to a maximum daily dose of 100 mg

Children: 6 – 12 years: 10 mg every 4 to 6 hours to a maximum daily dose of 25 mg

Elixir

Allergic disorder

Children: 6 - 12 years: 10 to 25 mL as a single dose at night, or 10 mL two to three times daily
Children: 2 – 5 years: 5 to 15 mL as a single dose at night, or 5 mL two to three times daily

Sedation

Children: 6 - 12 years: 10 to 25 mL as a single dose at night
Children: 2 – 5 years: 5 to 15 mL as a single dose at night

Travel sickness

Children: 6 -12 years: 10 mL
Children: 2 - 5 years: 5 mL
To be taken the night before travel and repeated after 6-8 hours on the following day if required.

Nausea and vomiting

Children: 6 – 12 years: 10 mL every 4 to 6 hours to a maximum daily dose of 25 mL
Children: 2 – 5 years: 5 mL every 4 to 6 hours to a maximum daily dose of 15 mL

4.3 CONTRAINDICATIONS

Promethazine is contraindicated for use in patients with a history of hypersensitivity to the drug substance, substances of similar chemical structure, other phenothiazines or hypersensitivity to the other ingredients in the formulation. Phenergan Sugar Free (orange flavour) Elixir should not be given to patients with allergies to sodium metabisulfite, sodium sulfite or sodium benzoate.

Promethazine is contraindicated for use in:

- children under 2 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 2 years of age. A wide range of weight-based doses of Phenergan have resulted in respiratory depression in these patients (see Section 4.4 Special warnings and precautions for use)
- lactating women
- patients taking monoamine oxidase inhibitors (MAOIs) up to 14 days previously (see Section 4.5 Interactions with other medicines and other forms of interactions)
- jaundice induced by other phenothiazine derivatives
- patients in coma or suffering from CNS depression of any cause or who have received high doses of other CNS depressants.

Refer to Section 4.5 Interactions with other medicines and other forms of interactions for additional information.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Caution is advised in patients with:

- cardiovascular disease
- acute or chronic respiratory impairment as promethazine may thicken or dry lung secretions and impair expectoration
- epilepsy
- hypertensive crisis
- narrow-angle glaucoma
- stenosing peptic ulcer
- symptomatic prostatic hypertrophy
- bladder neck obstruction
- pyloroduodenal obstruction

Hypersensitivity reactions including anaphylaxis, urticaria and angioedema have been reported with promethazine use. In case of allergic reaction, treatment with promethazine must be discontinued and appropriate symptomatic treatment initiated -Section 4.5

Promethazine should be avoided in patients with Parkinson's disease, hypothyroidism, cardiac failure, pheochromocytoma, myasthenia gravis, or prostate hypertrophy, or in patients with a history of agranulocytosis.

Caution must be exercised when using H1-antihistamines such as promethazine due to the risk of sedation.

Combined use with other sedative medicinal products is not recommended (see Section 4.5).

Promethazine may delay the early diagnosis of intestinal obstruction or increased intracranial pressure through the suppression of vomiting.

Promethazine may mask the warning signs of ototoxicity caused by ototoxic drugs e.g. salicylates.

Promethazine may increase the effects of alcohol. Alcohol should be avoided during treatment.

QT interval prolongation has been reported with phenothiazines.

Phenothiazine derivatives may potentiate QT interval prolongation which increases the risk of onset of serious ventricular arrhythmias of the torsade de pointes type, which is potentially fatal (sudden death). QT prolongation is exacerbated, in particular, in the presence of bradycardia, hypokalaemia, and acquired (i.e. drug induced) QT prolongation. If the clinical situation permits, medical and laboratory evaluations should be performed to rule out possible risk factors before initiating treatment with a phenothiazine derivative and as deemed necessary during treatment (see Section 4.8 Adverse effects (Undesirable effects).

Refer to 'Section 4.5 Interactions with other medicines and other forms of interactions' for additional information.

Prolonged administration of any phenothiazine may result in tardive dyskinesia, particularly in the elderly and children.

Alcohol and alcohol-containing medicines should be avoided while on this medicine (see section Section 4.5).
Phenothiazines may be additive with, or may potentiate the action of, other CNS depressants such as opiates or other analgesics, barbiturates or other sedatives, general anesthetics, or alcohol.

As agranulocytosis has been reported, regular monitoring of the complete blood count is recommended. The occurrence of unexplained infections or fever may be evidence of blood dyscrasia (see Section 4.5), and requires immediate haematological investigation.

All patients should be advised that, if they experience fever, sore throat or any other infection, they should inform their physician immediately and undergo a complete blood count. Treatment should be discontinued if any marked changes (hyperleucocytosis, granulocytopenia) are observed in the blood count.

There have been case reports of drug abuse with promethazine. The risk of abuse is greater in patients with a history of drug abuse.

As with neuroleptics, Neuroleptic Malignant Syndrome (NMS) characterised by hyperthermia, extrapyramidal disorders, muscle rigidity, altered mental status, autonomic nervous instability and

elevated CPK, may occur. As this syndrome is potentially fatal, promethazine must be discontinued immediately and intensive clinical monitoring and symptomatic treatment should be initiated.

Hypertensive crisis: Promethazine should be used with caution, if at all, in these patients.

Solar dermatitis has been reported following oral doses of Phenergan in patients with eczema or a tendency to rheumatism.

Due to the risk of photosensitivity, exposure to the sun or ultraviolet light should be avoided during or shortly after treatment.

Epilepsy: Epileptic patients may experience increased severity of convulsions.

Use in hepatic impairment

Caution is advised in patients with hepatic insufficiency. It should be avoided in patients with liver dysfunction.

Use in renal impairment

Caution is advised in patients with renal failure or insufficiency. It should be avoided in patients with renal dysfunction.

Use in the elderly

The elderly may experience paradoxical excitation with promethazine. The elderly are more likely to have CNS depressive side effects, including confusion and are more susceptible to the antimuscarinic effects of antihistamines, including hypotension (see Section 4.3 Contraindications).

Paediatric use

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

Caution should be exercised when administering promethazine to children 2 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 individualized weight-based dosing is used.

Concomitant administration of other drugs with respiratory depressant effects should be avoided.

The use of promethazine should be avoided in children and adolescents with signs and symptoms suggestive of Reye’s syndrome.

Excessive dosages of antihistamines in children may cause hallucinations, convulsions and sudden death. Children may experience paradoxical excitation with promethazine.

It is recommended that the lowest effective dose of Phenergan be used in paediatric patients 2 years of age or older.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Promethazine will enhance the action of any anticholinergic agent, tricyclic antidepressant, sedative or hypnotic. Promethazine may cause drowsiness and will enhance the sedative effects of CNS depressants (including alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives and neuroleptics), and have additive antimuscarinic actions with other antimuscarinic drugs (atropine, tricyclic antidepressants). Interactions between promethazine and monoamine oxidase inhibitors and tricyclic antidepressants (TCAs) may prolong and intensify the anticholinergic and CNS depressive effects. Alcohol should be avoided during treatment. Combination with alcohol enhances the sedative effects of H1 antihistamines. Promethazine may interfere with immunological urine pregnancy tests to produce false-positive or false-negative results.

Special caution is required when promethazine is used concurrently with drugs known to cause QT prolongation (such as antiarrhythmics, antimicrobials, antidepressants, antipshychotics) to avoid exacerbation of risk of QT prolongation.

Cytochrome P450 2D6 Metabolism: Some phenothiazines are moderate inhibitors of CYP2D6. There is a possible pharmacokinetic interaction between inhibitors of CYP2D6, such as phenothiazines, and CYP2D6 substrates. Co administration of promethazine with amitriptyline/ amitriptylinoxide, a CYP2D6 substrate, may lead to an increase in the plasma levels of amitriptyline/ amitriptylinoxide. Monitor patients for dose-dependent adverse reactions associated with amitriptyline/amitriptylinoxide.

Promethazine should be avoided in patients taking monamine oxidase inhibitors within the previous 14 days, and monamine oxidase inhibitors should be avoided while using promethazine.

Seizure threshold-lowering drugs: Concomitant use of seizure-inducing drugs or seizure threshold lowering drugs should be carefully considered due to the severity of the risk for the patient (see Section 4.4).

Gastro-intestinal agents that are not absorbed (magnesium, aluminium and calcium salts, oxides and hydroxides): Reduced gastro-intestinal absorption of phenothiazines may occur. Such gastrointestinal agents should not be taken at the same time as phenothiazines (at least 2 hours apart, if possible).

Drugs with anticholinergic properties: Concomitant use of promethazine with drugs with anticholinergic properties enhances the anticholinergic effect.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no relevant fertility data available in animals.

Use in pregnancy – Pregnancy Category C

The use of promethazine is not recommended during pregnancy and in women of childbearing potential not using contraception. Promethazine should be used in pregnancy only if the potential benefits to the patient are weighed against the possible risk to the foetus. Promethazine, owing to its pharmacological effects, has caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.

When promethazine has been given in high doses during late pregnancy, promethazine has caused prolonged neurological disturbances in the infant.

There are no available animal studies regarding reproductive toxicity.

Use in lactation

Promethazine is excreted in breast milk. There are risks of neonatal irritability and excitement. Therefore it should not be used for breastfeeding women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Promethazine considerably affects the ability to drive a vehicle and operate machines. Promethazine may cause drowsiness, dizziness and blurred vision and can considerably affect the ability of driving a vehicle and operating machines. Drowsiness may continue the following day. Those affected should not drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

CNS Effects

CNS depressive effects of promethazine include sedation and impaired performance (impaired driving performance, poor work performance, incoordination, reduced motor skills, and impaired information processing). Performance may be impaired in the absence of sedation and may persist the morning after a night-time dose.

The CNS stimulatory effects of promethazine may include anxiety, hallucinations, appetite stimulation, muscle dyskinesias and activation of epileptogenic foci.

High doses of promethazine may cause nervousness, tremor, insomnia, agitation, and irritability.

Anticholinergic Effects

Side effects of promethazine associated with cholinergic blockage include dryness of the eyes, mouth and nose, blurred vision, urinary hesitancy and retention, constipation and tachycardia.

More common reactions

Gastrointestinal disorders:	Dry mouth, epigastric distress, loss of appetite, nausea, vomiting, constipation, diarrhoea
Nervous system disorders:	Sedation or somnolence, restlessness, dizziness, lassitude, incoordination, fatigue
Eye disorders:	Blurred vision

Less common reactions

Cardiovascular:	Tachycardia, bradycardia, faintness
Skin and subcutaneous tissue disorders:	Contact dermatitis (topical), urticaria, angioneurotic oedema, pruritus
Haematological:	Leucopenia, agranulocytosis, aplastic anaemia, thrombocytopenic purpura
Nervous system disorders:	Tinnitus, euphoria, nervousness, insomnia, convulsive seizures, oculogyric crises, excitation, catatonic-like states, hysteria, tardive dyskinesia
Respiratory:	Marked irregular respiration

Reactions with frequency unknown

Skin and subcutaneous tissue disorders:	Rash, Photosensitivity
Hepatobiliary disorders:	Jaundice cholestatic
Renal and Urinary Disorders:	Urinary retention
Nervous system disorders:	Neuroleptic Malignant Syndrome, somnolence, dizziness, headaches, tic-like movements of the head and face, extrapyramidal symptoms including muscle spasm. Dystonia, including oculogyric crisis, usually transitory are commoner in children and young adults, and usually occur within the first 4 days of treatment or after dosage increases. Anticholinergic effects such as ileus paralytic, risk of urinary retention, dry mouth, constipation, accommodation disorder. The elderly are particularly susceptible to

	the anticholinergic effects and confusion due to promethazine
Immune system disorders:	Allergic reactions, including anaphylactic reaction, urticaria, rash, pruritus, angioedema and anaphylactic reaction have been reported
Metabolism and nutrition disorders:	Anorexia, decreased appetite
Blood and lymphatic system disorders:	Blood dyscrasias including haemolytic anaemia, agranulocytosis, leukopenia, eosinophilia, thrombocytopenia (including thrombocytopenic purpura)
Psychiatric disorders:	Agitation, confusional state, anxiety. Infants, newborns and premature are susceptible to the anticholinergic effects of promethazine, while other children may display paradoxical hyperexcitability, restlessness, nightmares, disorientation
Cardiac disorders:	Palpitations, arrhythmias, QT Prolongation, torsade de pointes
Respiratory, thoracic and mediastinal disorders	Respiratory depression, nasal congestion
Vascular disorders:	Hypotension
General disorders and administration site conditions:	Tiredness

Severe or life-threatening reactions

Agranulocytosis, anaphylaxis.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

Symptoms of severe overdosage are variable. The chief sign of acute poisoning from ingestion of an overdose of Phenergan is unconsciousness, which is commonly delayed. In addition, convulsions, hallucinations, delirium, acute anxiety, psychotic reactions, extreme hyperaesthesia and hyperalgesia with extensor plantar responses may occur. Anticholinergic action may cause tachycardia, flushed skin, dry mouth and sometimes mydriasis and urinary retention.

In adults, CNS depression is more common, with drowsiness, coma, convulsions, progressing to respiratory failure or cardiovascular collapse.

High doses can cause ventricular arrhythmias including QT prolongation and torsade de pointes (see Section 4.8 Adverse effects (Undesirable effects).

In infants and children, CNS stimulation predominates over CNS depression causing ataxia, excitement, tremors, psychoses, hallucinations, convulsions and possibly hyperpyrexia, which may be followed by deepening coma and cardiorespiratory collapse.

Treatment

Similar to that of other phenothiazines. In the event of overdose of promethazine, take all appropriate measures immediately. For information on the management of overdose, contact the Poisons Information Centre (in Australia call 13 11 26).

Symptomatic supportive therapy is indicated and maintenance of adequate ventilation should be instituted if necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Promethazine, a phenothiazine derivative, is a long acting antihistamine with mild atropine-like anticholinergic effects and some antiserotonin effects, and because of its marked effect on the central nervous system (CNS), it acts as an antiemetic, hypnotic, tranquilliser, and a potentiator of anaesthetics, hypnotics, sedatives and analgesics.

Clinical trials

No data available

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Promethazine is well absorbed after oral administration. Peak plasma concentrations are reached 2 to 3 hours after administration by this route, although there is low systemic bioavailability after oral administration, due to high first-pass metabolism in the liver.

Distribution

Promethazine crosses the blood-brain barrier and the placenta, and is distributed into breast milk. It is highly bound to plasma proteins (76-93%).

Metabolism

Promethazine undergoes extensive metabolism, predominantly to promethazine sulfoxide, and also to N-desmethylpromethazine.

Excretion

It is excreted slowly via the urine and bile, mainly as metabolites. Elimination half-lives of 5 to 14 hours have been reported. The antihistamine action has been reported to be between 4 and 12 hours.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available

Carcinogenicity

No data available

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Phenergan Elixir contains sodium benzoate, sodium sulfite, sodium metabisulfite, maltitol solution, acesulfame potassium, sodium citrate dihydrate, citric acid monohydrate, ascorbic acid, caramel, purified water and orange juice flavour 510844E.

Phenergan Tablets contain lactose monohydrate, maize starch, povidone, magnesium stearate, hypromellose, macrogol 200 and opaspray blue M-1-4210A.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Elixir: Store below 25°C. Protect from light.

Tablets: Store below 30°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Elixir: 100 mL bottle

Tablets: 10 mg tablets are available in blister packs of 50 tablets.

25 mg tablets are available in blister packs of 50 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

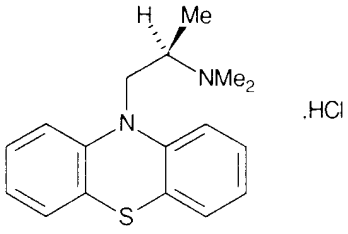
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Promethazine hydrochloride is a white or faintly yellow, practically odourless, crystalline powder. It is very soluble in water, freely soluble in alcohol and in chloroform, and practically insoluble in ether.

Chemical structure

Promethazine hydrochloride has the following structural formula:



CAS number

58–33-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Elixir, Tablets: Pharmacist Only Medicine (Schedule 3)

8 SPONSOR

Sanofi Consumer Healthcare
87 Yarraman Place
Virginia
Australia
Toll Free Number (medical information): 1800 818 806
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

24 October 1997

10 DATE OF REVISION

27 May 2022

Summary table of changes

Section changed	Summary of new information
4.3	New contraindications added as per CCDS v5
4.4	New warnings added per CCDS v5
4.5	New interactions with medicines and other interactions added as per CCDS v5
4.6	Update to fertility and pregnancy sections in line with CCDS v5
4.7	Additional information added in line with CCDS latest update
4.8	Additional AEs added to align with CCDs v5
4.9	In relation to overdose additional information included as per CCDS v5