# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Prothiazine 25 mg

Prothiazine Syrup

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25mg of the active substance Promethazine hydrochloride.

Each 1ml syrup contains 1mg of the active substance Promethazine hydrochloride.

For full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Prothiazine tablets are purple, round, and biconvex.

Prothiazine syrup is a clear orange-colored liquid.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Antihistaminic, Antiemetic, Sedative.

### 4.2 Posology and method of administration

Route of administration: Oral.

Not for use in children under the age of 2 years (see section 4.3).

**For treatment of allergies:**

Children aged 2-5 years:

5-15 ml of syrup in one dose, to be taken at night or 5 ml two to three times a day. Do not administer more than 15 ml per day.

Children aged 6-12 years:

10-25 ml of syrup in one dose to be taken at night, or 10 ml twice a day. Do not administer more than 25 ml per day.

Children above the age of 12 and adults:

Begin treatment by taking one tablet at night. The dosage can be increased to a maximum of one tablet twice a day, as required.

**For treatment and prevention of nausea and vomiting:**

Children aged 2-5 years:

5 ml of syrup every 4-6 hours up to a maximum of 15 ml per day.

Children aged 6-12 years:

A dose of 10 ml of syrup; wait 4-6 hours before administering another dose. Up to two doses per day can be administered (a total of 20 ml per day).

Children above the age of 12 and adults:

One tablet every 4-6 hours, up to a maximum of 4 tablets per day.

**For short-term use as a sedative, with the doctor's instruction only:**

Children aged 2-5 years:

5-15 ml of syrup as a single dose to be taken at night, at bedtime.

Children aged 6-12 years:

10-20 ml of syrup as a single dose to be taken at night, at bedtime.

Children above the age of 12 and adults:

One to three tablets as a single dose, to be taken at night, at bedtime.

**4.3 Contraindications**

- Prothiazine should not be given to patients with a known hypersensitivity to the active substance promethazine, other phenothiazines or to any of the excipients listed in section 6.1.
- Prothiazine should not be used in patients in coma or suffering from CNS depression of any cause.
- Promethazine is contraindicated for use in children less than two years of age.
- Prothiazine should be avoided in patients taking monoamine oxidase inhibitors up to 14 days previously.

**4.4 Special warnings and precautions for use**

Hypersensitivity reactions including anaphylaxis, urticaria and angioedema have been reported with Prothiazine use. In case of allergic reaction, treatment with Prothiazine must be discontinued and appropriate symptomatic treatment initiated (see Section 4.8).
Prothiazine should be avoided in patients with liver or renal dysfunction, Parkinson's disease, hypothyroidism, cardiac failure, pheochromocytoma, myasthenia gravis, or prostate hypertrophy, or in patients with a history of narrow angle glaucoma or agranulocytosis.

Caution must be exercised when using $H_1$-antihistamines such as Prothiazine due to the risk of sedation. Combined use with other sedative medicinal products is not recommended (see section 4.5).

Prothiazine should not be used for longer than 7 days without seeking medical advice.
Caution should be used in patients with:

- Asthma, bronchitis or bronchiectasis. Prothiazine may thicken or dry lung secretions and impair expectoration.
- Severe coronary artery disease
- Epilepsy
- Bladder neck or pyloro-duodenal obstruction.

<u>Ototoxicity</u>
Promethazine may mask the warning signs of ototoxicity caused by ototoxic drugs e.g. salicylates. It may also delay the early diagnosis of intestinal obstruction or raised intracranial pressure through the suppression of vomiting.

QT prolongation
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, hypokalemia, 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).

Photosensitivity reactions
Due to the risk of photosensitivity, exposure to strong sunlight or ultraviolet light should be avoided during or shortly after treatment (see section 4.8).

Paediatric population
The use of promethazine should be avoided in children and adolescents with signs and symptoms suggestive of Reye's Syndrome.

Excipient(s) with known effect

Prothiazine tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Prothiazine syrup contain sucrose, sorbitol and glucose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Alcohol and alcohol-containing medicines should be avoided while on this medicine (see 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.

The occurrence of unexplained infections or fever may be evidence of blood dyscrasia (see section 4.8), and requires immediate hematological 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.

**4.5 Interaction with other medicinal products and other forms of interaction**

Prothiazine will enhance the action of any anticholinergic agent, tricyclic antidepressant, sedative or hypnotic.

Alcohol should be avoided during treatment. Combination with alcohol enhances the sedative effects of H1 antihistamines.

Prothiazine may interfere with immunological urine pregnancy tests to produce false-positive or false-negative results.

Prothiazine should be discontinued at least 72 hours before the start of skin tests as it may inhibit the cutaneous histamine response thus producing false negative results.

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

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

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 gastro-intestinal 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 Prothiazine with drugs with anticholinergic properties enhances the anticholinergic effect.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
The use of Prothiazine is not recommended during pregnancy and in women of childbearing potential not using contraception, unless the potential benefits outweigh the potential risks. When promethazine has been given in high doses during late pregnancy, promethazine has caused prolonged neurological disturbances in the infant.

Advise patients to inform their healthcare provider of a known or suspected pregnancy. Advise patients to avoid becoming pregnant while receiving this medicine. Advise female patients of reproductive potential to use effective contraception.

There are no available animal studies regarding reproductive toxicity.

Breast-feeding
Prothiazine is excreted in breast milk (see section 5.2). There are risks of neonatal irritability and excitement. Prothiazine is not recommended for use in breast-feeding.

Fertility
There are no relevant fertility data in animals.

## 4.7 Effects on ability to drive and use machines

Because the duration of action may be up to 12 hours, patients should be advised that if they feel drowsy, dizzy and have blurred vision, they should not drive or operate heavy machinery.

**4.8 Undesirable effects**

*The following CIOMS frequency rating is used: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/1000 to <1/1000); very rare (<1/10,000), not known (cannot be estimated from the available data).*

Immune system disorders
Frequency not known: Allergic reactions, including anaphylactic reaction, urticaria, angioedema.

Skin and subcutaneous tissue disorders
Frequency not known: Rash, photosensitivity reaction .

Nervous system disorders
Very common: Sedation or somnolence
Frequency not known: Dizziness, headaches, extrapyramidal effects including restless legs syndrome, muscle spasms and tic-like movements of the head and face.
Frequency not known: 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.
Frequency not known: 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.
Frequency not known: children less than 6 years of age also experienced psychomotor hyperactivity.

Psychiatric disorders
Frequency not known: Agitation, confusional state, anxiety.
Frequency not known: Infants, newborns and premature are susceptible to the anticholinergic effects of promethazine, while other children may display paradoxical hyperexcitability, restlessness, nightmares, disorientation
Frequency not known: children less than 6 years of age also experienced aggression and hallucination.

Eye disorders
Frequency not known: Blurred vision

Gastrointestinal disorders
Frequency not known: Epigastric irritation/ discomfort, dry mouth

Renal and urinary disorders
Frequency not known: urinary retention

Metabolism and nutrition disorders
Frequency not known: Decreased appetite

Cardiac disorders
Frequency not known: Palpitations, arrhythmias (including QT prolongation and torsade de pointes)

Vascular disorders
Frequency not known: Hypotension

Respiratory, thoracic and mediastinal disorders

Frequency not known: Respiratory depression (see Section 4.4), nasal congestion

Hepatobiliary disorders
Frequency not known: jaundice cholestatic

Blood and lymphatic system disorders
Frequency not known: Blood dyscrasias including haemolytic anaemia, agranulocytosis leukopenia, eosinophilia, thrombocytopenia (including thrombocytopenic purpura).

General and administration site conditions
Frequency not known: Tiredness

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

**4.9 Overdose**

Symptoms
Symptoms of severe overdosage are variable. They are characterised in children by various combinations of excitation, ataxia, incoordination, athetosis and hallucinations, intellectual disability and cognition deficit in children less than 6 years of age while adults may become drowsy and lapse into coma. Convulsions may occur in both adults and children: coma or excitement may precede their occurrence. Tachycardia may develop. Cardiorespiratory depression is uncommon. High doses (supratherapeutic doses) can cause ventricular arrhythmias including QT prolongation and torsade de pointes (see section 4.8).

Management
If the patient is seen soon enough after ingestion, it should be possible to induce vomiting with ipecacuanha despite the antiemetic effect of promethazine; alternatively, gastric lavage may be used.

Treatment is otherwise supportive with attention to maintenance of adequate respiratory and circulatory status. Convulsions should be treated with diazepam or another suitable anticonvulsant.

In the event of overdose of Prothiazine, take all appropriate measures immediately.

## 5. PHARMACOLOGICAL PROPERTIES

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antihistamines for systemic use; Phenothiazine derivatives, ATC code: R06AD02

Potent, long acting, antihistamine with additional anti-emetic central sedative and anti-cholinergic properties.

**5.2 Pharmacokinetic properties**

Promethazine is distributed widely in the body. It enters the brain and crosses the placenta. Promethazine is slowly excreted via urine and bile. Phenothiazines pass into the milk at low concentrations.

**5.3 Preclinical safety data**

No additional pre-clinical data of relevance to the prescriber.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Prothiazine tablets: Lactose, Maize starch, Methocel E5, Povidone 25, Magnesium stearate, Purified talc, Diethyl Phthalate, Propylene glycol, Polyvinyl acetate phthalate, Colloidal silicone dioxide, Titanium dioxide, Indigo carmine, Ponceau 4R.

Prothiazine syrup: Sucrose, sorbitol solution, Liquid glucose, Disodium hydrogen Phosphate, Ethanol, Ascorbic acid, Citric acid, Orange flavour 926, Methyl hydroxybenzoate, Propyl hydroxybenzoate, Sunset yellow, Purified water.

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Prothiazine syrup: Shelf life after first opening: 22 days

### 6.4 Special precautions for storage

Store below 25ºC.

## 7. MARKETING AUTHORISATION HOLDER and MANUFACTURER

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