SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Prothiazine Expectorant Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contain:

Promethazine Hydrochloride 5 mg, Guaiphenesin 45 mg, Ipecacuanha 10 mg

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Prothiazine Expectorant syrup is a clear, orange liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For temporary relief of cough due to colds, allergies.

4.2 Posology and method of administration

Route of administration: Oral.

The generally accepted dosage is:

For adults and children over 10 years old: 10-15 ml 2-3 times a day.

For children between 6 and 10 years old: 5 ml 2-3 times a day.

This medicine is not intended for children and babies under 6 years of age

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Prothiazine Expectorant should not be used in patients:

- In coma or suffering from CNS depression of any cause.
- In children under the age of 6 years.
- In patients taking monoamine oxidase inhibitors up to 14 days previously.
- In shock, at risk of seizure, or with cardiovascular disorders.
- With impaired renal hepatic or cardiac function.

4.4 Special warnings and precautions for use

Prothiazine Expectorant may thicken or dry lung secretions and impair expectoration.

It should therefore be used with caution in patients with asthma, bronchitis or bronchiectasis.

Use with care in patients with severe coronary artery disease, narrow angle glaucoma, epilepsy or hepatic and renal insufficiency.

Caution should be exercised in patients with bladder neck or pyloro-duodenal obstruction.

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

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.

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).

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).

Use with care in patients who suffer from chronic cough, have asthma or is suffering from an acute asthma attack.

Do not give with a cough suppressant or any other cough and cold medicine.

Ipecac is cardio active and so should be avoided by patients on anti-arrhythmic drugs. It should be avoided by diabetics.

Prothiazine Expectorant should not be used for longer than 7 days without seeking medical advice.

Excipients with known effect

Prothiazine Expectorant 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

If urine is collected within 24 hours of a dose of Prothiazine Expectorant, a metabolite of guaifenesin may cause a colour interference with laboratory determinations of urinary 5-hydroxyindoleacetic acid (5-HIAA) and vanillylmandelic acid (VMA).

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.

Whilst unlikely at recommended doses, there is a theoretical risk of interaction of Ipecac with anti-arrhythmic drugs.

4.6 Fertility, pregnancy and lactation

Pregnancy

Promethazine should not be used in pregnancy unless the physician considers it essential. The use of Prothiazine Expectorant is not recommended in the 2 weeks prior to delivery in view of the risk of irritability and excitement in the neonate.

There are no or limited amount of data from the use of Guaifenesin in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Guaifenesin is not recommended during pregnancy and in women of childbearing potential not using contraception.

No information or evidence is available on the safe use of ipecac during pregnancy is available.

Breastfeeding

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.

Guaifenesin is excreted in breast milk in small amounts. There is insufficient information on the effects of Guaifenesin in breastfed newborns/infants. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Prothiazine Expectorant therapy, taking into account the benefit of breast -feeding for the child and the benefit of therapy for the woman.

No information or evidence is available on the safe use of ipecac during lactation is available.

Fertility

There is insufficient information available to determine whether guaifenesin has the potential to impair fertility.

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 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 (≥1/10 00 to <1/1000); very rare (<1/10 000), not known (cannot be estimated from the available data).

Promethazine

Immune system disorders
Allergic reactions, including urticaria, rash, pruritus and anaphylactic reactions have been reported.
Skin and subcutaneous tissue disorders
Photosensitive skin reactions have been reported.

Nervous system disorders
Somnolence, dizziness, headaches, extrapyramidal effects including restless legs syndrome, muscle spasms and tic-like movements of the head and face.
The elderly are particularly susceptible to the anticholinergic effects and confusion due to promethazine

Psychiatric disorders
Restlessness, nightmares, and disorientation. Infants (newborn and premature) are susceptible to the anticholinergic effects of promethazine, while other children may display paradoxical hyperexcitability.

Eye disorders
Blurred vision

Gastrointestinal disorders
Epigastric irritation/ discomfort, dry mouth

Renal and urinary disorders
urinary retention

Metabolism and nutrition disorders
Anorexia

Cardiac disorders
Palpitations, arrhythmias (including QT prolongation and torsade de pointes)

Vascular disorders
Hypotension

Hepatobiliary disorders
jaundice

Blood and lymphatic system disorders
Blood dyscrasias including haemolytic anaemia rarely occur. Agranulocytosis.

General and administration site conditions
Tiredness

Adverse Drug Reactions Identified during Clinical Trials, Epidemiology studies and Post-Marketing Experience with Guaifenesin:
Immune system disorders: Hypersensitivity reactions (hypersensitivity, pruritus and urticaria), Rash – Incidence: Not known
Gastrointestinal disorders: Abdominal pain upper, Diarrhoea, Nausea, Vomiting – Incidence: Not known

Ipecac is generally well tolerated at recommended doses but large doses and chronic usage may cause gastric irritation, nausea, vomiting, diarrhoea and cardiac conduction abnormalities.

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, 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).

The effects of acute toxicity from guaifenesin may include gastrointestinal discomfort, nausea and drowsiness. When taken in excess, guaifenesin may cause renal calculi.

Large doses of ipecacuanha may irritate the gastrointestinal tract, and give rise to nausea, persistent bloody vomiting or bloody diarrhoea.
Mucosal erosions of the entire gastrointestinal tract have been reported

Overdosage is unlikely as a result of the emetic action of ipecacuanha,
however, if emetine is absorbed in sufficient amounts it may have adverse effects on the heart, such as conduction abnormalities or myocardial infarction. These symptoms may also be combined with dehydration due to vomiting, and may cause vasomotor collapse followed by death.

Management

If the patient is seen soon enough after ingestion of promethazine, 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 other suitable anticonvulsant.

Acute overdosage of ipecacuanha should be treated with activated charcoal to delay absorption. Prolonged vomiting should be controlled by intramuscular injection of antiemetics. Supportive measures should be taken to correct fluid and electrolyte imbalance and cardiac effects.

5. PHARMACOLOGICAL PROPERTIES

Promethazine

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.

Guaifenesin

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Expectorants, ATC code: R05CA03

Guaifenesin is thought to exert its pharmacological action by stimulating receptors in the gastric mucosa. This increases the output from secretory glands of the gastrointestinal system and reflexly increases the flow of fluids from glands lining the respiratory tract. The result is an increase in volume and decrease in viscosity of bronchial secretions. Other actions may include stimulating vagal nerve endings in bronchial secretory glands and stimulating certain centres in the brain, which in turn enhance respiratory fluid flow. Guaifenesin produces its expectorant action within 24 hours.

5.2 Pharmacokinetic Properties

Absorption

Guaifenesin is well absorbed from the gastro-intestinal tract following oral administration, although limited information regarding its pharmacokinetics is available. After the administration of 600 mg guaifenesin to healthy adult volunteers, the Cmax was approximately 1.4 ug/ml, with tmax occurring approximately 15 minutes after drug administration.

Distribution

No information is available on the distribution of guaifenesin in humans.

Metabolism and elimination

Guaifenesin appears to undergo both oxidation and demethylation. Following an oral dose of 600 mg guaifenesin to 3 healthy male volunteers, the t½ was approximately 1 hour and the drug was not detectable in the blood after approximately 8 hours.

Pharmacokinetics in Renal/Hepatic Impairment

There have been no specific studies of guaifenesin in subjects with renal or hepatic impairment.

Caution is therefore recommended when administering this product to subjects with severe renal or hepatic impairment.

Pharmacokinetics in the Elderly

Not applicable.

5.3. Preclinical Safety Data

Mutagenicity

There is insufficient information available to determine whether guaifenesin has mutagenic potential.

Carcinogenicity

There is insufficient information available to determine whether guaifenesin has carcinogenic potential.

Teratogenicity

There is insufficient information available to determine whether guaifenesin has teratogenic potential.

Fertility

There is insufficient information available to determine whether guaifenesin has the potential to impair fertility.

Ipecacuanha

5.1 Pharmacodynamic properties

Ipecac acts according to its principal alkaloids emetine and cephaeline.

Namely as a reflex expectorant.

5.2 Pharmacokinetic properties

Ipecac is absorbed as emetine, which may cause adverse effects on the heart such as conduction abnormalities or myocardial infarction. There is the possibility of the accumulation of emetine causing cardiotoxicity and myopathy. Emetine is slowly metabolised and excreted in the urine and faeces.

5.3 Preclinical safety data

None available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, Sorbitol Solution 70%, Liquid Glucose 80%, Citric Acid, Ethanol 96%, Ascorbic Acid, Orange oil 926., Monosodium Glutamate, Saccharin Sodium, Methyl Hydroxybenzoate, Disodium Hydrogen Phosphate, Propyl Hydroxybenzoate, Sunset yellow FCF, Purified Water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

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

Shelf life after first opening: 2 months

6.4 Special precautions for storage

Store below 25ºC.

7. MARKETING AUTHORISATION HOLDER and MANUFACTURER

CTS CHEMICAL INDUSTRIES LTD, ISRAEL

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