DILOSYN EXPECTORANT
Methdilazine, Ammonium Chloride and Sodium Citrate Expectorant

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml (one teaspoonful) contains:

- Methdilazine Hydrochloride USP 2.5 mg
- Ammonium Chloride IP 0.1 g
- Sodium Citrate IP 50 mg
- Colour: Caramel USPNF
- In a flavoured syrup base containing Menthol IP

PHARMACEUTICAL FORM

Syrup for oral administration

CLINICAL PARTICULARS

Therapeutic Indications

For symptomatic treatment of cough.

Posology and Method of Administration

Route of Administration

For oral administration only.

Adults and children 12 years of age and above: 15 ml syrup 3 to 4 times daily.

Children 6-12 years of age: 8 ml syrup 3 to 4 times daily.

Children below 6 years of age: Not recommended.

Elderly

No relevant data available.

Renal Impairment

See section Contraindications.

Hepatic Impairment

See section Contraindications.

Contraindications
**DILOSYN EXpectorant** is contraindicated in patients with:

- bone marrow depression,
- comatose patients,
- hypersensitivity to any of the ingredients or other phenothiazines,
- jaundice,
- newborn or premature infants,
- acutely ill and dehydrated children,
- nursing mothers,
- concomitant use with central nervous system depressants,
- renal and hepatic impairment.

**Special Warnings and Special Precautions for Use**

Use **DILOSYN EXPECTORANT** with caution in patients suffering from:

- Asthma
- Acute or chronic respiratory impairment, especially children
- Bladder neck obstruction
- Cardiovascular disease
- Liver dysfunction
- History of ulcer disease
- Narrow-angle glaucoma
- Prostatic hypertrophy
- Pyloroduodenal obstruction
- Stenosing peptic ulcer
- Elderly people have increased vulnerability to adverse effects from any CNS-active chemical. First-generation H1 antihistamines have potential to cross the blood-brain barrier, impair neurotransmission at CNS H1 receptors, and cause adverse CNS effects such as drowsiness, confusion, and agitation.
- Do not use to sedate children.
- Use with caution in children with epilepsy.
- Should be avoided in children with acute porphyria.
- Should be used with caution in children with urinary retention, glaucoma, or pyloroduodenal obstruction.
- Citrate salts taken orally can enhance the absorption of aluminium from the gastrointestinal tract (see section Undesirable Effects). Patients with impaired renal function are particularly susceptible to aluminium accumulation and citrate-containing oral preparations are best avoided by patients with renal failure taking aluminium-containing compounds.

**Interaction with Other Medicaments and Other Forms of Interaction**

**Alcohol**

There is an increase in sedative effect when alcohol is administered with first generation antihistamines.

**Belladonna**

The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with a phenothiazine. Increased manic, agitated reactions, or enhanced anticholinergic effects resulting in cardiorespiratory failure can occur especially in cases of belladonna overdose. Excessive anticholinergic activity may be
manifested by dry mouth, constipation, urinary retention, tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. Benzodiazepines, short-acting barbiturates, or chloral hydrate may be used to sedate patients with anticholinergic toxicity.

**Betel Nut**

Increased extrapyramidal side effects of phenothiazines can occur due to cholinergic effect of betel nut.

**Dehydroepiandrosterone**

Elevated Dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to phenothiazines. If DHEA is elevated, treatment with dexamethasone 1 mg orally may be used to normalize DHEA levels.

**Duloxetine**

Duloxetine is a moderately potent inhibitor of CYP2D6; therefore its coadministration with a phenothiazine is likely to increase bioavailability of the phenothiazine leading to elevated phenothiazine plasma concentrations, increasing the risk of adverse events such as sedation, confusion, cardiac arrhythmias, orthostatic hypotension, hyperthermia, extrapyramidal effects. Use caution when prescribing duloxetine with phenothiazines.

**Evening Primrose**

Evening primrose oil may reduce the seizure threshold when taken with phenothiazines.

**Hydrocodone, Oxycodone**

Use caution with the concomitant use of hydrocodone or oxycodone and a CNS depressant such as phenothiazines may result in additive CNS effects and increase the risk of respiratory depression, profound sedation, coma, and/or death. Reduce initial hydrocodone dose by 20% to 30% and consider using a lower dose of phenothiazines when co-administering. Start oxycodone at one-third to one-half of the usual dosage when coadministered with phenothiazines. Monitor patients for signs of respiratory depression, sedation, or hypotension.

**Levomethadyl**

There may be an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest). Levomethadyl is contraindicated in patients being treated with DILOSYN EXPECTORANT as it may precipitate QT prolongation.

**Phenylalanine**

Interaction may result in increased incidence of tardive dyskinesia. Abnormal phenylalanine metabolism in certain patients may lead to phenylalanine accumulation in the brain and in turn, reduced brain availability of other large neutral amino acids. This may interfere with the synthesis of catecholamines. Caution is advised if phenylalanine is administered with a neuroleptic agent. Monitor the patient closely for signs of tardive dyskinesia.
**Teduglutide**

Coadministration of teduglutide with a phenothiazine, may significantly increase absorption of phenothiazine. Phenothiazines dose reduction may be necessary when administered concomitantly with teduglutide. Monitor for increased phenothiazine side effects if a patient is taking teduglutide concomitantly with an oral phenothiazine.

**Drug-Lab Modifications**

Urine chorionic gonadotrophin measurement - Interpret pregnancy test results with caution in patients receiving phenothiazines due to the possibility of false-negative or false-positive results for tests based on immunological reactions between human chorionic gonadotropin (HCG) and anti-HCG. Drug therapy should be evaluated when interpreting pregnancy test results.

**Pregnancy and Lactation**

**Pregnancy**

Either animal-reproduction studies have not demonstrated a foetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters). It is unknown if the drug crosses placenta.

There is no good evidence of an association between first trimester exposure to ammonium chloride and foetal abnormalities.

Because animal reproduction studies are not always predictive of human response, *DILOSYN EXPECTORANT* should be used during pregnancy only if clearly needed.

**Lactation**

Infant risk cannot be ruled out. Available evidence and/or expert consensus inconclusive or is inadequate for determining infant risk when used during breastfeeding. *DILOSYN EXPECTORANT* is contraindicated in nursing mothers. (See section *Contraindications*)

**Effects on Ability to Drive and Use Machines**

The most prominent effect of phenothiazine derivatives is drowsiness. Use of *DILOSYN EXPECTORANT* can interfere with ability to drive and use machines.

**Undesirable Effects**

The following adverse events have been noted with the ingredients of *DILOSYN EXPECTORANT*.

**Cardiovascular**

The most common cardiovascular effect from the use of phenothiazine derivatives is postural hypotension. Other effects include bradyarrhythmia, tachyarrhythmia, reflex tachycardia,
cardiac arrest, electrocardiogram changes including blunting of T waves and prolongation of the Q-T interval. The elderly are especially sensitive to postural hypotension and syncope.

**Dermatologic**

Dermatitis, photosensitivity, urticaria, pigmentation of the skin, especially exposed areas, with prolonged use of phenothiazine derivatives at high doses.

**Endocrine/Metabolic**

Induction of lactation, increased appetite and weight gain. Large doses of ammonium chloride may cause a profound acidosis and hypokalaemia. Excessive doses of sodium salts may also lead to sodium overloading and hyperosmolality.

**Gastrointestinal**

Constipation, diarrhea, epigastric distress, increased appetite, weight gain, loss of appetite (anorexia), nausea, vomiting and xerostomia. Ammonium salts are irritant to the gastric mucosa and may produce nausea and vomiting particularly in large doses. Excessive oral doses of citrate salts may have a laxative effect.

**Hematologic**

Agranulocytosis, leukopenia, thrombocytopenic purpura.

**Hepatic**

Jaundice, both reversible and chronic.

**Immunologic**

Anaphylactoid reactions and lupus erythematosus.

**DILOSYN EXPECTORANT** contains sodium metabisulfite which may cause allergic-type anaphylactic reactions and life-threatening or less severe asthmatic episodes.

**Neurologic**

Asthenia, lassitude, diplopia, dizziness, incoordination, insomnia, neuritis, seizures, tremors, somnolence. The most prominent effect of phenothiazine derivatives is drowsiness. Extrapyramidal reactions may occur, especially in high doses. The elderly are especially sensitive to this effect.

The elderly are prone to akathisia, persistent dyskinesia, confusional states. Newborn or premature infants, acutely ill and dehydrated children, and nursing mothers may demonstrate increased susceptibility to dystonias.

**Ophthalmic**

Blurred vision. Prolonged administration at high dosage of phenothiazine derivatives may result in lenticular opacities and corneal opacities, vision impairment, pigmentary retinopathy and epithelial keratopathies.
Otic
Tinnitus.

Psychiatric
Dissociative Catatonia-like states disorder, hysteria, euphoria, excitation, nervousness.

Renal
Dysuria, urinary frequency and urinary retention.

Reproductive
Early menses, sexual dysfunction (decreased libido and inhibition of ejaculation).

Respiratory
Laryngeal edema, thickening of bronchial secretions, tightness of the chest, asthma, wheezing and nasal congestion.

Other
Angioneurotic edema and fatigue.

Overdose

Symptoms and signs

Mild to moderate poisoning with antihistamines: somnolence, anticholinergic, effects (ie, mydriasis, flushing, fever, dry mouth, and decreased bowel sounds), tachycardia, mild hypertension, and nausea and vomiting are common after overdose. Agitation, confusion, and hallucinations may develop with moderate poisoning.

Severe poisoning with antihistamines: Severe effects may include agitated delirium, psychosis, seizures, coma, hypotension, QRS widening, and ventricular dysrhythmias, including torsade de pointe but are generally only reported in adults after very large, deliberate ingestions. Rhabdomyolysis and renal failure may rarely develop in patients with prolonged agitation, coma, or seizures.

Vital signs: Tachycardia is common. Hyperthermia, hypotension, and hypertension have been reported.

Large doses of ammonium chloride may cause a profound acidosis and hypokalaemia. Ammonium salts are irritant to the gastric mucosa and may produce nausea and vomiting particularly in large doses. Excessive doses of sodium salts may also lead to sodium overloading and hyperosmolality. Excessive oral doses of citrate salts may have a laxative effect.

Treatment
**Monitoring:** Monitor vital signs (including temperature) and mental status. No specific laboratory work is needed in most patients. Obtain an ECG and institute continuous cardiac monitoring in patients with moderate to severe toxicity (i.e. agitation delirium, seizures, coma, and hypotension). Monitor creatinine phosphokinase in patients with prolonged agitation, seizures or coma; monitor renal function urine output in patients with rhabdomyolysis.

**Management of Mild to Moderate Toxicity:** Supportive care; give activated charcoal if patient presents shortly after ingestion; sedate with benzodiazepines for agitation and delirium. Hypertension and tachycardia are generally mild and well tolerated, and do not require specific treatment.

**Management of Severe Toxicity:** Orotracheal intubation for airway protection should be performed early. Prehospital decontamination not recommended because of potential for somnolence and seizures. For dermal exposure, remove patches and wash skin thoroughly. Gastric lavage may be of benefit, administer activated charcoal if patient presents soon after a large ingestion. Severe delirium require large doses of benzodiazepines for sedation (doses greater than 10 mg of lorazepam). Seizures (may rarely progress to status epilepticus) may require aggressive use of benzodiazepines, propofol and/or barbiturates. Monitor for QRS widening and ventricular dysrhythmias; treat with intravenous sodium bicarbonate (1 to 2 mEq/kg IV bolus starting dose, titrate to blood pH 7.45 to 7.55), or lidocaine if sodium bicarbonate unsuccessful. Monitor core temperature and treat hyperthermia with aggressive benzodiazepine sedation to control agitation and external cooling. Clinical manifestations may be prolonged due to delayed absorption in the setting of an anticholinergic ileus. Antidote, physostigmine is indicated to reverse the CNS effects. Long lasting reversal of anticholinergic signs and symptoms is generally not achieved because of relatively short duration of action of physostigmine. It is most often used diagnostically to distinguish anticholinergic delirium from other causes of altered mental status. Hemodialysis or hemoperfusion are of no value.

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamic Properties**

Methdilazine is a potent, long-acting antipruritic agent and is effective in relieving various itching conditions. Methdilazine is a reasonably potent antibradykinin agent.

**Mechanism of Action**

**Methdilazine**

Methdilazine is phenothiazine with antihistaminic actions. Antihistamines competitively interferes with the binding of histamine at the H1 receptor. As a result the actions of histamine on vascular and respiratory smooth muscle is diminished. In addition, antihistamines bind to H1 receptors in the central nervous system, resulting in drowsiness, dystonias, or stimulation.

**Ammonium chloride**

Ammonium chloride has an irritant effect on mucous membranes and are considered to have expectorant properties.

**Sodium Citrate**

Sodium citrate is considered to increase bronchial secretion by salt action.
Pharmacokinetic Properties

**Methdilazine**

**Metabolism**
Main site of metabolic transformation is liver. H1 blockers are among the many drugs that induce hepatic microsomal enzymes, and they may facilitate their own metabolism.

**Absorption, Distribution & Excretion**
Well absorbed after oral administration. The H1 antagonists are well absorbed from the GI tract. Following oral administration, peak plasma concentration is achieved in 2 to 3 hr H1 antagonists are eliminated more rapidly by children than by adults and more slowly in those with severe liver disease.

**Ammonium Chloride**
Ammonium salts are effectively absorbed from the gastrointestinal tract. The ammonium ion is converted into urea in the liver; the anion thus liberated into the bloodstream and extracellular fluid causes a metabolic acidosis and decreases the pH of the urine, this is followed by a transient diuresis.

**Preclinical Safety Data**
No relevant data available.

**PHARMACEUTICAL PARTICULARS**

**List of Excipients**
Sucrose, Sodium Benzoate, Propylene Glycol, Sodium Metabisulphite, Citric Acid, Vanillin, Flavour Caramel, Caramel, Menthol, Oil Anise and Purified Water.

**Incompatibilities**
No incompatibilities have been identified.

**Shelf Life**
The expiry date is indicated on the label and packaging.

**Special Precautions for Storage:**
Store in a well closed container at temperature not exceeding 30°C. Protect from direct sunlight.

Keep out of reach of children.

**Nature and Specification of Container**
Amber glass bottle.
All presentations may not be marketed in the Country.

**Instructions for Use / Handling**

There are no special requirements for use or handling of this product.

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**Adapted from:**


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