DILOSYN SYRUP / DILOSYN TABLETS

Methdilazine Syrup / Methdilazine Hydrochloride Tablets USP

QUALITATIVE AND QUANTITATIVE COMPOSITION

DILOSYN SYRUP

Each 5 ml (one teaspoonful) contains:
Methdilazine Hydrochloride USP 4 mg
in a flavoured syrup base
Colour: Caramel USPNF

DILOSYN TABLETS

Each sugar coated tablet contains:
Methdilazine Hydrochloride USP 8 mg
Colours: Sunset Yellow Lake and Titanium Dioxide IP

PHARMACEUTICAL FORM

Syrup.
Sugar coated tablet.

CLINICAL PARTICULARS

Therapeutic Indications

For the treatment of allergic rhinitis, atopic dermatitis (effective in relieving pruritic symptoms), drug-induced rash, eczema, neurodermatitis, pruritus ani, pruritus of vulva and urticaria and for the symptomatic relief of contact dermatitis including contact dermatitis due to poison ivy and pityriasis rosea.

Posology and Method of Administration

Route of Administration

For oral administration only.

Adults

8 mg (10 ml syrup or 1 tablet) 2 to 4 times daily.

Children

4 mg (5 ml syrup) 2 to 4 times daily.

Not for use in children younger than 2 years of age.
**Renal impairment**

No relevant data available.

**Hepatic impairment**

Should be avoided in children with severe liver disease as there is increased risk of coma.

**Contraindications**

*DILOSYN* is contraindicated in patients with bone marrow depression, hypersensitivity to methdilazine or other phenothiazines, jaundice, comatose patients, newborn or premature infants, acutely ill and dehydrated children, nursing mothers, concomitant use with central nervous system depressants.

**Special Warnings and Special Precautions for Use**

Use *DILOSYN* cautiously 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.

**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; its coadministration with a phenothiazine is likely to increase bioavailability of the phenothiazine leading to elevated phenothiazine serum 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 since this 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) due to interaction with methdilazine. Therefore, levomethadyl is contraindicated in patients being treated with DILOSYN 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**

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

**Lactation**

Infant risk cannot be ruled out. Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. **DILOSYN** 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** can interfere with ability to drive and use machines.

**Undesirable Effects**

**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.

**Gastrointestinal**

Constipation, diarrhea, epigastric distress, increased appetite, weight gain, loss of appetite (Anorexia), nausea, vomiting and xerostomia (dry mouth).

**Hematologic**

Agranulocytosis, leukopenia, thrombocytopenic purpura.

**Hepatic**

Jaundice, both reversible and chronic.

**Immunologic**

Anaphylactoid reactions and lupus erythematosus. Methdilazine syrup 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:* 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.

**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 is a 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.

Pharmacokinetic Properties

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 hours. H1 antagonists are eliminated more rapidly by children than by adults and more slowly in those with severe liver disease.

Preclinical Safety Data

No relevant data available.

PHARMACEUTICAL PARTICULARS

List of Excipients

**DILOSYN SYRUP**

Sucrose, glucose liquid, sodium citrate, citric acid monohydrate, benzoic acid, sodium metabisulphite, propylene glycol, caramel, flavour peach (colourless), vanillin, purified water.

**DILOSYN TABLETS**

Lactose, starch maize, dibasic calcium phosphate, acacia powder, methyl hydroxybenzoate, propyl hydroxybenzoate, ethyl hydroxybenzoate, magnesium stearate,
purified water, colour sunset yellow lake, talc purified, titanium dioxide, sucrose, carnauba wax, white bees wax, dichloromethane.

Incompatibilities

No incompatibilities have been identified.

Shelf Life

**DILOSYN SYRUP / DILOSYN TABLETS**

The expiry date is indicated on the label and packaging.

Special Precautions for Storage

**DILOSYN SYRUP**

Store in a well closed container at temperatures not exceeding 30ºC, protected from direct sunlight.

Keep out of reach of children.

**DILOSYN TABLETS**

Store in a dry place at temperatures not exceeding 30ºC. Protect from direct sunlight.

Keep out of reach of children.

Nature and Specification of Container

**DILOSYN SYRUP**

Amber glass bottle.

**DILOSYN TABLETS**

Strips of tablets in a carton.

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.

For further information please contact:

GlaxoSmithKline Pharmaceuticals Limited

Registered Office

Dr. Annie Besant Road, Worli

Mumbai 400 030, India.

Trade marks are owned by or licensed to the GSK group of companies
Adapted from:


- Recommendations for "Methdilazine hydrochloride, Ammonium Chloride, Sodium Citrate" PI Review received from the SERM team vide email dated 19-Dec-2016.