Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Dicyclomine Injection IP

(Brand Name: MEFTAL-SPAS® Injection)

2. Qualitative and Quantitative Composition

Each ml contains:

Dicyclomine Hydrochloride IP …….. 10 mg

Benzyl Alcohol IP (as preservative) ……..……. 2% v/v

Water for Injection IP ……..…... q.s.

3. Dosage Form and Strength

Dosage Form: Injection.

Dosage Strength: Dicyclomine hydrochloride 10 mg per ml (20 mg/ 2 ml ampoule).

4. Clinical Particulars

4.1 Therapeutic Indication

MEFTAL-SPAS Injection is indicated for the treatment of gastrointestinal (GI) spasm, particularly that associated with functional irritable bowel syndrome (IBS).

4.2Posology and Method of Administration

Adults: MEFTAL-SPAS Injection must be administered via intramuscular (I.M.) route only.

Do not administer by I.V. or any other route. The recommended dose of dicyclomine is 10 mg to 20 mg up to four times a day.

Treatment with dicyclomine injection should not be given for more than 2 days; if necessary, treatment can be continued with oral formulation.

Or, as prescribed by the Physician.

Pharmaceutical Precautions

Each ampoule is for single use only. Solution should be used immediately after opening the ampoule. The unused portion, if any, should be discarded.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if solution is not clear or has suspended matter.

Aspirate the syringe before injecting to avoid intravascular injection, since thrombosis may occur if the drug is inadvertently injected intravascularly.

4.3Contraindications

MEFTAL-SPAS Injection is contraindicated in the following:

- Hypersensitivity to dicyclomine or to any component of the formulation.
- Infants less than 6 months of age.
- Nursing mothers.
- In patients with:
    - Unstable cardiovascular status in acute hemorrhage.
    - Myasthenia gravis.
    - Glaucoma.
    - Obstructive uropathy.
    - Obstructive disease of the gastrointestinal tract (GIT).
    - Severe ulcerative colitis.
    - Reflux esophagitis.

4.4Special Warnings and Precautions for Use

Test Dose: Before therapy with MEFTAL-SPAS Injection is instituted, a test dose is recommended to ascertain possibility of hypersensitivity to ingredients of MEFTAL-SPAS Injection. Serious acute hypersensitivity reactions may require the use of subcutaneous epinephrine and other emergency measures.

Cardiovascular Conditions: Dicyclomine hydrochloride needs to be used with caution in conditions characterized by tachyarrhythmia such as thyrotoxicosis, congestive heart failure and in cardiac surgery, where they may further accelerate the heart rate. Investigate any tachycardia before administration of dicyclomine. Care is required in patients with coronary heart disease (CHD), as ischemia and infarction may be worsened, and in patients with hypertension.

Peripheral and Central Nervous System (CNS): The peripheral effects of dicyclomine are a consequence of their inhibitory effect on muscarinic receptors of the autonomic nervous system. They include dryness of the mouth with difficulty in swallowing and talking, thirst, reduced bronchial secretions, dilatation of the pupils (mydriasis) with loss of accommodation (cycloplegia) and photophobia, flushing and dryness of the skin, transient bradycardia followed by tachycardia, with palpitations and arrhythmias, and difficulty in micturition, as well as reduction in the tone and motility of the GI tract leading to constipation.

In the presence of high environmental temperature heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). It should also be used cautiously in patients with fever. If symptoms occur, the drug should be discontinued and supportive measures instituted. Because of the inhibitory effect on muscarinic receptors within the autonomic nervous system, caution should be taken in patients with autonomic neuropathy. CNS signs and symptoms include confusion, disorientation, short-term amnesia, hallucinations, dysarthria, ataxia, coma, euphoria, fatigue, insomnia, agitation and mannerisms, and inappropriate affect. Psychosis has been reported

in sensitive individuals given anticholinergic drugs. These CNS signs and symptoms usually resolve within 12 to 24 hours after discontinuation of the drug.

Myasthenia Gravis: With overdose, a curare-like action may occur (i.e., neuromuscular blockade leading to muscular weakness and possible paralysis). It should not be given to patients with myasthenia gravis except to reduce adverse muscarinic effects of an anticholinesterase.

Intestinal Obstruction: Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance, treatment with this drug would be inappropriate and possibly harmful.

Rarely development of Ogilvie's syndrome (colonic pseudo-obstruction) has been reported. Ogilvie's syndrome is a clinical disorder with signs, symptoms, and radiographic appearance of an acute large bowel obstruction but with no evidence of distal colonic obstruction.

Toxic Dilatation of Intestine (megacolon): Toxic dilatation of intestine and intestinal perforation is possible when anticholinergic agents are administered in patients with *Salmonella* dysentery.

Ulcerative Colitis: Caution should be taken in patients with ulcerative colitis. Large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon. Dicyclomine is contraindicated in patients with severe ulcerative colitis.

Prostatic Hypertrophy: Dicyclomine should be used with caution in patients with known or suspected prostatic enlargement, in whom prostatic enlargement may lead to urinary retention.

4.5Drug Interactions

Antiglaucoma Agents: Anticholinergics antagonize the effects of antiglaucoma agents. Anticholinergic drugs in the presence of increased intraocular pressure may be hazardous when taken concurrently with agents such as corticosteroids. Use of dicyclomine in patients with glaucoma is not recommended.

Other Drugs with Anticholinergic Activity: The following agents may increase certain actions or side effects of anticholinergic drugs including dicyclomine: Amantadine, antiarrhythmic agents of Class I (e.g., quinidine), antihistamines, antipsychotic agents (e.g., phenothiazines), benzodiazepines, MAO inhibitors, narcotic analgesics (e.g., meperidine), nitrates and nitrites, sympathomimetic agents, tricyclic antidepressants, and other drugs having anticholinergic activity.

Other GI Motility Drugs: Interaction with other GI motility drugs may antagonize the effects of drugs that alter GI motility, such as metoclopramide.

Effect on Absorption of Other Drugs: Anticholinergic agents may affect GI motility and may affect the absorption of various drugs, such as slowly dissolving dosage forms of digoxin; increased serum digoxin concentration may result.

Effect on Gastric Acid Secretion: The inhibitory effects of anticholinergic drugs on gastric hydrochloric acid secretion are antagonized by agents used to treat achlorhydria and those used to test gastric secretion.

4.6Use in Special Populations

Pregnant Women

Pregnancy Category B. Adequate and well-controlled studies have not been conducted with dicyclomine in pregnant women at the recommended doses. Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the fetus due to dicyclomine. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lactating Women

Dicyclomine hydrochloride is excreted in human milk. Because of the potential for serious adverse reactions in infants, dicyclomine is contraindicated in lactating women.

Pediatric Patients

Safety and effectiveness in pediatric patients have not been established. Dicyclomine is contraindicated in infants less than 6 months of age.

Geriatric Patients

Dicyclomine hydrochloride should be used with caution in the elderly, as they may be more susceptible to its adverse effects. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Hepatic and Renal Impairment Patients

Dicyclomine should be used with caution in patients with known hepatic and/or renal impairment.

4.7Effect on Ability to Drive and Use Machines

Dicyclomine hydrochloride may produce drowsiness, dizziness or blurred vision. The patient should be warned not to engage in activities requiring mental alertness, such as driving or operating machinery or performing hazardous work while taking dicyclomine.

4.8Undesirable Effects

The pattern of adverse effects seen with dicyclomine is mostly related to its pharmacological actions at muscarinic receptors. They are a consequence of the inhibitory effect on muscarinic receptors within the autonomic nervous system. These effects are dose-related and are usually reversible when treatment is discontinued.

The most serious adverse reactions reported with dicyclomine hydrochloride include cardiovascular and CNS symptoms. The most common adverse reactions (> 5% of patients) are dizziness, dry mouth, blurred vision, nausea, somnolence, asthenia and nervousness. The following adverse reactions have been reported with use of dicyclomine:

- Cardiac disorders: Palpitations, tachyarrhythmias.
- Eye disorders: Cycloplegia, mydriasis, blurred vision.

- GI disorders: Abdominal distension, abdominal pain, constipation, dry mouth, dyspepsia, nausea, vomiting.
- General disorders and administration site conditions: Fatigue, malaise.
- Immune system disorders: Drug hypersensitivity including face edema, angioedema, anaphylactic shock.
- Nervous system disorders: Dizziness, headache, hallucinations, insomnia, somnolence, syncope.
- Psychiatric disorders: Confusional state, nervousness.
- Reproductive system and breast disorders: Suppressed lactation.
- Respiratory, thoracic and mediastinal disorders: Dyspnoea, nasal congestion.
- Skin and subcutaneous tissue disorder: Allergic dermatitis, erythema, rash.

4.9Overdose

The signs and symptoms of overdose include headache, nausea, vomiting, blurred vision, dilated pupils, hot and dry skin, dizziness, dryness of the mouth, difficulty in swallowing, and CNS stimulation including convulsion. A curare-like action may occur (i.e., neuromuscular blockade leading to muscular weakness and possible paralysis).

It is not known if dicyclomine is dialyzable. Treatment should consist of gastric lavage, emetics, and activated charcoal. Sedatives (e.g., short-acting barbiturates, benzodiazepines) may be used for management of overt signs of excitement. If indicated, an appropriate parenteral cholinergic agent may be used as an antidote.

5. Pharmacological Properties

5.1 Mechanism of Action

Dicyclomine is a tertiary amine antispasmodic and anticholinergic (antimuscarinic) agent. Dicyclomine relieves smooth muscle spasm of the GI tract. Animal studies indicate that this action is achieved via a dual mechanism:

1. A specific anticholinergic effect (antimuscarinic) at the acetylcholine-receptor sites with approximately 1/8 the milligram potency of atropine (in vitro, guinea pig ileum); and
2. A direct effect upon smooth muscle (musculotropic) as evidenced by dicyclomine's antagonism of bradykinin- and histamine-induced spasms of the isolated guinea pig ileum.

5.2Pharmacodynamic Properties

Dicyclomine hydrochloride exerts antispasmodic and anticholinergic effects. Dicyclomine relieve spasm of smooth muscles, inhibit the secretion of saliva and sweat, decrease GI secretions and motility, dilate the pupils, increase heart rate, and depress motor function.

5.3Pharmacokinetic Properties

Intramuscular injection is about twice as bioavailable as oral dosage forms. Kinetic studies of dicyclomine in injectable formulations are not reported. In human, pharmacokinetic data of dicyclomine by oral route is as follows:
Dicyclomine is rapidly absorbed after oral administration, reaching peak values within 60 to 90 minutes. Mean volume of distribution for a 20 mg oral dose is approximately 3.65 l/kg suggesting extensive distribution in tissues. The metabolism of dicyclomine has not been studied. The principal route of excretion is via the urine (79.5% of the dose). Excretion also occurs in the feces, but to a lesser extent (8.4%). Mean half-life of plasma elimination in one study was determined to be approximately 1.8 hours when plasma concentrations were measured for 9 hours after a single dose. In subsequent studies, plasma concentrations were followed for up to 24 hours after a single dose, showing a secondary phase of elimination with a somewhat longer half-life.

6. Nonclinical Properties

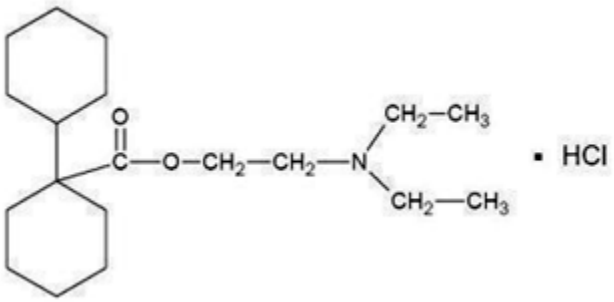
6.1 Animal Toxicology

In studies in rats at doses of up to 100 mg/kg/day, dicyclomine produced no deleterious effects on breeding, conception, or parturition. Reproduction studies have been performed in rats and rabbits at doses of up to 33 times the maximum recommended human dose based on 160 mg/day (3 mg/kg) and have revealed no evidence of harm to the fetus due to dicyclomine. Long-term animal studies have not been conducted to evaluate the carcinogenic potential of dicyclomine.

7. Description

MEFTAL-SPAS Injection is clear colourless to almost colourless solution filled in 2 ml clear glass ampoule with snap off red ring.
Each ml of MEFTAL-SPAS Injection contains 10 mg of dicyclomine hydrochloride for I.M. use.

Dicyclomine hydrochloride is an antispasmodic and anticholinergic agent. Dicyclomine hydrochloride occurs as a fine, white, crystalline, practically odorless powder with a bitter taste. It is soluble in water, freely soluble in alcohol and chloroform, and very slightly soluble in ether.
Molecular Weight: 345.95 g/mol.
Molecular Formula: $C_{19}H_{35}NO_2 \cdot HCl$.
Chemical Name: [bicyclohexyl]-1-carboxylic acid, 2-(diethylamino) ethyl ester, hydrochloride.
Structural Formula:



Inactive ingredients (excipients) of MEFTAL-SPAS Injection contain EDTA Sodium, Sodium Metabisulphite, Sodium Chloride, Benzyl Alcohol, and Sodium Hydroxide Pellets.

8. Pharmaceutical Particulars

8.1 Incompatibilities

MEFTAL-SPAS Injection should not be mixed with solutions for which physical and chemical compatibility has not been established. In particular, this applies to alkaline solutions as a precipitate may form.

8.2Shelf-life

24 months.

8.3Packaging Information

2 ml glass ampoule for single use.

8.4Storage and Handling Instructions

Store protected from light.
Keep out of reach of children.

9. Patient Counseling Information

Administration Instructions

- MEFTAL-SPAS Injection is for intramuscular (I.M.) administration only. Do not administer by any other route. Inadvertent administration may result in thrombosis or thrombophlebitis, and injection site reactions such as pain, edema, skin color change and even reflex sympathetic dystrophy syndrome.
- Inform parents and caregivers not to use MEFTAL-SPAS Injection in infants less than 6 months of age.
- Advice lactating women that MEFTAL-SPAS Injection should not be used while breastfeeding their infant.
- In the presence of a high environmental temperature, heat stroke can occur (due to decreased sweating) with use of dicyclomine. If symptoms occur, instruct patients to discontinue the drug and seek immediate medical help.
- MEFTAL-SPAS Injection may produce drowsiness or blurred vision. The patient should be warned not to engage in activities requiring mental alertness, such as driving a motor vehicle or operating machinery while taking dicyclomine.
- Advise patients to stop medicine and contact their healthcare provider as soon as possible if they develop any type of rash or if hypersensitivity/allergic reaction (e.g., difficulty breathing, swelling of the face) occur.

10.Details of Manufacturer

Nitin Lifesciences Ltd.,
Rampur Road, Paonta Sahib, Dist. Sirmour,
Himachal Pradesh – 173 025, India.

11. Details of Permission or License Number with Date

Manufacturing license No. MB/05/209 dated 20/09/2006.

12. Date of Revision

January 2021.

Marketed by:
BLUE CROSS LABORATORIES PVT LTD.
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