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

Prescribing Information

1. Generic Name

Mefenamic Acid and Dicyclomine Hydrochloride Tablets IP
(Brand Name: MEFTAL-SPAS ® Tablets / MEFTAL-SPAS ® DS Tablets)

2. Qualitative and Quantitative Composition

MEFTAL-SPAS Tablets
Each uncoated tablet contains:
Mefenamic Acid IP ……. 250 mg
Dicyclomine Hydrochloride IP ……... 10 mg
Colour: Tartrazine.

MEFTAL-SPAS DS Tablets
Each uncoated tablet contains:
Mefenamic Acid IP …… 500 mg
Dicyclomine Hydrochloride IP …….. 20 mg
Colour: Tartrazine.

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Mefenamic acid 250 mg / 500 mg + dicyclomine hydrochloride 10 mg / 20 mg per tablet respectively.

4. Clinical Particulars

4.1 Therapeutic Indication

MEFTAL-SPAS Tablets / MEFTAL-SPAS DS Tablets are indicated for abdominal pain and dysmenorrhea.

4.2 Posology and Method of Administration

For oral administration in adults and adolescents.
MEFTAL-SPAS Tablets: 1 to 2 tablets to be administered three times daily.
MEFTAL-SPAS DS Tablets: 1 tablet to be administered three times daily.

Treatment is generally required till the time dysmenorrhea symptoms persist i.e., 3 to 5 days during the menses. Therapy should not be given for longer than 7 days at a time. MEFTAL-SPAS / MEFTAL-SPAS DS Tablets should be taken preferably with or after food.
Or, as prescribed by the physician.

4.3 Contraindications

MEFTAL-SPAS / MEFTAL-SPAS DS Tablets are contraindicated in the following:

- Known hypersensitivity to mefenamic acid or to dicyclomine or to any component of the formulation.
- Pre-existing asthma and aspirin-sensitive asthma.
- Active ulceration/bleeding or chronic inflammation of upper or lower gastrointestinal (GI) tract.
- Treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.
- Pre-existing renal disease/obstructive uropathy.
- Glaucoma.
- Myasthenia gravis.
- Last trimester of pregnancy.
- Lactation.
- Inflammatory bowel disease, paralytic ileus and intestinal atony.

4.4 Special Warnings and Precautions for Use

Mefenamic Acid

Cardiovascular Thrombotic Events: Clinical trials of several cyclooxygenase-2 (COX-2) selective and nonselective non-steroidal anti-inflammatory drugs (NSAIDs) of up to 3 years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction (MI), and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

Hypertension: NSAIDs, including mefenamic acid, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDS, including mefenamic acid, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema: Fluid retention and edema have been observed in some patients taking NSAIDs. Mefenamic acid should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal Effects - Risk of Ulceration, Bleeding, and Perforation: NSAIDs, including mefenamic acid, can cause serious GI adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. NSAIDs should be prescribed with extreme

caution in those with a prior history of ulcer disease or GI bleeding. Patients with a prior history of peptic ulcer disease and/or GI bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anti-coagulants, longer duration of NSAID therapy, smoking, consuming alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population. To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Hepatic Effects: Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, including mefenamic acid. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately 3 or more times the upper limit of normal - ULN) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with mefenamic acid. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), mefenamic acid should be discontinued.

Renal Effects: Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injuries. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. No information is available for controlled studies regarding the use of mefenamic acid in patients with advanced renal disease. Therefore, treatment with mefenamic acid is not recommended in these patients with advanced renal disease.

Anaphylactoid Reactions: As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to mefenamic acid. Mefenamic acid should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions: NSAIDs, including mefenamic acid, can cause serious cutaneous adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Hematological Effects: Anemia is sometimes seen in patients receiving NSAIDs, including mefenamic acid. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including mefenamic acid, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia. NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving mefenamic acid who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Preexisting Asthma: Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, mefenamic acid should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Drug / Laboratory Test Interactions: Mefenamic acid may prolong prothrombin time. Therefore, when the drug is administered to patients receiving oral anticoagulant drugs, frequent monitoring of prothrombin time is necessary. A false-positive reaction for urinary bile, using the diazo tablet test, may result after mefenamic acid administration. If biliuria is suspected, other diagnostic procedures, such as the Harrison spot test, should be performed.

Dicyclomine Hydrochloride

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 hydrochloride. Care is required in patients with coronary heart disease, as ischemia and infarction may be worsened, and in patients with hypertension.

Peripheral and Central Nervous System: The peripheral effects of dicyclomine hydrochloride 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.
Central nervous system (CNS) signs and symptoms include confusional state, disorientation, amnesia, hallucinations, dysarthria, ataxia, coma, euphoria, fatigue, insomnia, agitation and mannerisms, and inappropriate affect. Psychosis and delirium have been reported in sensitive individuals (such as elderly patients and/or in patients with mental illness) given anticholinergic drugs. These CNS signs and symptoms usually resolve within 12 to 24 hours after discontinuation of the drug.
Myasthenia Gravis: With overdosage, 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.

4.5 Drug Interactions

Mefenamic Acid

Cytochrome P450 (CYP) Inhibitors: A number of compounds are inhibitors of CYP2C9. Drug interactions studies of mefenamic acid and these compounds have not been conducted. The possibility of altered safety and efficacy should be considered when mefenamic acid is used concomitantly with these drugs.
Angiotensin Converting Enzyme (ACE) Inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.
Aspirin/NSAID: When mefenamic acid is administered with aspirin, its protein binding is reduced, although the clearance of free mefenamic acid is not altered. The clinical

significance of this interaction is not known. However, as with other NSAIDs, concomitant administration of mefenamic acid and aspirin or any other NSAID is not generally recommended because of the potential of increased adverse effects.

Diuretics: Clinical studies, as well as observations during the post-approval period, have shown that mefenamic acid can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy of NSAIDs, the patient should be observed closely for signs of renal failure, as well as to assure diuretic efficacy.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate: NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Warfarin: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

Antacids: In a single dose study, ingestion of an antacid containing 1.7 gram of magnesium hydroxide with 500 mg of mefenamic acid resulted in the peak plasma concentration (C_{max}) and area under curve (AUC) of mefenamic acid increasing by 125% and 36%, respectively.

Aminoglycosides (Amikacin, Tobramycin, Gentamicin, etc.): NSAIDs/mefenamic acid increases plasma concentration of aminoglycosides by decreasing its renal clearance. Also, reduction in renal function (in susceptible individuals) decreases elimination of aminoglycosides and increases its serum levels. Monitor serum aminoglycosides levels whenever mefenamic acid is used concomitantly.

Cardiac Glycosides (Digoxin): NSAIDs may exacerbate cardiac failure, reduces glomerular filtration rate (GFR) and increases plasma cardiac glycoside levels. Further, concomitant use of mefenamic acid with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin. Thus, during concomitant use of mefenamic acid and digoxin, monitor serum digoxin levels.

Oral Hypoglycemic Agents: NSAIDs may inhibit metabolism of sulfonylurea drugs, thereby prolongs half-life and increases risk of hypoglycemia. Thus, caution should be exercised while administration of mefenamic acid and sulfonylurea drugs (such as glimepiride, gliclazide, glibenclamide, etc.) concomitantly.

Antiplatelet Drugs: NSAIDs can interfere with platelet function; thus, administration of mefenamic acid with antiplatelet drugs (such as aspirin or clopidogrel) may increase risk of GI ulceration or bleeding. When GI bleeding or ulceration occurs, mefenamic acid therapy should be withdrawn.

Ciclosporin: Concomitant use of mefenamic acid and ciclosporin may increase risk of nephrotoxicity associated with ciclosporin. During concomitant use of mefenamic acid and ciclosporin, monitor patients for signs of worsening renal function.
Corticosteroids: Concomitant use of NSAIDs with corticosteroids increases risk of GI ulceration or bleeding. When GI bleeding or ulceration occurs, mefenamic acid therapy should be withdrawn immediately.
Mifepristone: As NSAIDs can reduce the effects of mifepristone, mefenamic acid should not be taken for 8 to 12 days after mifepristone administration.
Quinolone Antibiotics: Animal data indicates that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.
Tacrolimus: When NSAIDs are given with tacrolimus, risk of nephrotoxicity increases. Thus, when mefenamic acid and ciclosporin are used concomitantly, renal function should be monitored.
Zidovudine: There is increased risk of hematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of hemarthrosis and hematoma in human immunodeficiency (HIV) positive hemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Dicyclomine Hydrochloride
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, monoamine oxidase (MAO) inhibitors, narcotic analgesics (e.g., meperidine), nitrates and nitrites, sympathomimetic agents, tricyclic antidepressants, and other drugs having anticholinergic activity.
Other Gastrointestinal Motility Drugs: Interaction with other gastrointestinal motility drugs may antagonize the effects of drugs that alter gastrointestinal motility, such as metoclopramide.
Antacids: Because antacids may interfere with the absorption of anticholinergic agents including dicyclomine, simultaneous use of these drugs should be avoided.
Effect on Absorption of Other Drugs: Anticholinergic agents may affect gastrointestinal absorption of various drugs by affecting gastrointestinal motility, such as slowly dissolving dosage forms of digoxin thus, increased serum digoxin concentration may occur.
Effect on Gastric Acid Secretion: The inhibitory effects of anticholinergic drugs on gastric acid secretion are antagonized by agents used to treat achlorhydria and those used to test gastric secretion.

4.6 Use in Special Populations

Pregnant Women

Mefenamic Acid: Pregnancy Category C; Dicyclomine: Pregnancy Category B. For this combination product, there are no adequate and well controlled studies available in pregnant women. Congenital abnormalities have been reported with use of NSAIDs in humans; however, these are low in frequency and do not appear to follow any discernible pattern. In view of the known effects of NSAIDs on the fetal cardiovascular system (risk of premature closure of the ductus arteriosus), use of mefenamic acid in the last trimester of pregnancy is contraindicated. The onset of labor may be delayed and the duration increased with an increased bleeding tendency in both mother and child. NSAIDs, including mefenamic acid, should not be used during the first two trimesters of pregnancy or labor unless the potential benefit to the patient outweighs the possible risk to the fetus.

Epidemiological studies in pregnant women with products containing dicyclomine hydrochloride (at doses up to 40 mg/day) have not shown that dicyclomine hydrochloride increases the risk of fetal abnormalities if administered during the first trimester of pregnancy. Reproduction studies have been performed in rats and rabbits at doses of up to 100 times the maximum recommended dose (based on 60 mg/day for an adult person) and have revealed no evidence of impaired fertility or harm to the fetus due to dicyclomine. Since the risk of teratogenicity cannot be excluded with absolute certainty for any product, the drug should be used during pregnancy only if clearly needed.

MEFTAL-SPAS / MEFTAL-SPAS DS Tablets should not be used during the first two trimesters of pregnancy unless the potential benefit to the patient outweighs the possible risk to the fetus. MEFTAL-SPAS / MEFTAL-SPAS DS Tablets are contraindicated for use in the third trimester of pregnancy.

Lactating Women

Trace amounts of mefenamic acid may be present in breast milk and transmitted to the nursing infant. But, the risk to the infant seems to be limited. Dicyclomine has been reported to be excreted in human milk. Use of dicyclomine is contraindicated in nursing mothers. Because of the potential for serious adverse reactions in nursing infants, MEFTAL-SPAS / MEFTAL-SPAS DS Tablets are contraindicated for use in lactation. If drug therapy is essential to mother, breast-feeding must be discontinued during treatment period.

Paediatric Patients

This formulation is not intended for use in children as there is no feasibility of dosage adjustments. Both, mefenamic acid and dicyclomine are not recommended in infants less than 6 months of age. It is advised that children under 12 years of age should use paediatric formulations of these drugs.

Geriatric Patients

Elderly patients with normal renal function may be given the same dose as recommended for adults. Dicyclomine hydrochloride should be used with caution in elderly who may be more susceptible to its adverse effects. The elderly patients have an increased frequency of adverse reactions to NSAIDs especially GI bleeding and perforation which may be fatal. Thus, as like other NSAIDs, caution should be exercised while use of mefenamic acid in elderly

population (> 65 years). Mefenamic acid is known to be substantially excreted by the kidney, and the risk of toxic reactions to it may be greater in patients with impaired renal function. 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.

Renal Impairment Patients
MEFTAL-SPAS / MEFTAL-SPAS DS Tablets should not be administered to patients with preexisting renal disease or in patients with significantly impaired renal function.

Hepatic Impairment Patients
MEFTAL-SPAS / MEFTAL-SPAS DS Tablets should be used with caution in patients with hepatic dysfunction.

4.7 Effect on Ability to Drive and Use Machines
Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs including mefenamic acid. Dicyclomine may produce drowsiness, dizziness or blurred vision. Thus, patients should be warned not to engage in activities requiring mental alertness, such as operating a motor vehicle or other machinery or performing hazardous work while taking this formulation.

4.8 Undesirable Effects
Mefenamic Acid
GI Disorders: The most commonly observed adverse events are GI in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur. Nausea, vomiting, diarrhea, flatulence, constipation, dyspepsia, abdominal pain, malaena, hematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease have been reported following administration. Less frequently, gastritis has been observed. Elderly or debilitated patients seem to tolerate GI ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. Anorexia, colitis, enterocolitis, gastric ulceration with or without hemorrhage, pancreatitis, steatorrhea may occur.
Blood and Lymphatic System Disorders: Hemolytic anemia (reversible), hypoplastic bone marrow, decrease in hematocrit, thrombocytopenic purpura, temporary lowering of white blood cell (WBC) count (leukopenia) with a risk of infection, sepsis, and disseminated intravascular coagulation. Agranulocytosis, aplastic anemia, eosinophilia, neutropenia, pancytopenia, thrombocytopenia may occur.
Immune System Disorders: Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of non-specific allergic reactions and anaphylaxis; respiratory tract reactivity comprising asthma, bronchospasm, or dyspnea; or, assorted skin disorders including rashes of various types, pruritus, urticaria, purpura, angioedema, and more rarely exfoliative or bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Metabolism and Nutritional Disorders: Glucose intolerance in diabetic patients, hypernatremia may occur.
Psychiatric Disorders: Confusion, depression, hallucinations, nervousness can develop, *albeit* rarely.
Nervous System Disorders: Optic neuritis, headaches, paresthesia, dizziness, drowsiness, reports of aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation have been reported. Blurred vision, convulsions, insomnia may occur.
Eye Disorders: Eye irritation, reversible loss of color vision, visual disturbances may occur.
Ear and Labyrinth Disorders: Ear pain, tinnitus, vertigo may occur.
Cardiac/Vascular Disorders: Edema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (e.g., myocardial infarction or stroke). Palpitations and hypotension may occur.
Respiratory, Thoracic, and Mediastinal Disorders: Asthma, dyspnea have been reported.
Hepato-Biliary Disorders: Borderline elevations of one or more liver function tests, cholestatic jaundice have been reported. Mild hepatotoxicity, hepatitis, hepatorenal syndrome may occur.
Skin and Subcutaneous Tissue Disorders: Angioedema, laryngeal edema, erythema multiforme, face edema, bullous reactions including Lyell's syndrome (toxic epidermal necrolysis) and Stevens-Johnson syndrome, perspiration, rash, photosensitivity reaction, pruritus, and urticaria.
Renal and Urinary Disorders: Allergic glomerulonephritis, acute interstitial nephritis, dysuria, hematuria, nephrotic syndrome, non-oliguric renal failure (particularly in dehydration), proteinuria, renal failure including renal papillary necrosis.
General Disorders: Fatigue, malaise, multi-organ failure, pyrexia may occur.
Investigations: A positive reaction in certain tests for bile in the urine of patients receiving mefenamic acid has been demonstrated to be due to the presence of the drug and its metabolites and not to the presence of bile.

Dicyclomine Hydrochloride

Most adverse reactions reported in clinical trials conducted with dicyclomine were typically anti-cholinergic in nature such as dry mouth, dizziness, blurred vision, nausea, light-headedness, drowsiness, weakness, and nervousness.
Other adverse reactions reported with dicyclomine and pharmacologically similar drugs, e.g., other anti-cholinergics and antispasmodics were:
Gastrointestinal: Vomiting, constipation, bloated feeling, abdominal pain, taste loss, anorexia may occur.
Central Nervous System: Tingling, headache, numbness, mental confusion and/or excitement (especially in elderly persons), dyskinesia, lethargy, syncope, speech disturbance, insomnia have been reported.
Ophthalmologic: Diplopia, mydriasis, cycloplegia, increased ocular tension.

Dermatologic/Allergic: Rash, urticaria, itching, and other dermal manifestations; severe allergic reaction or drug idiosyncrasies including anaphylaxis.
Genitourinary: Urinary hesitancy, urinary retention.
Cardiovascular: Tachycardia, palpitations.
Respiratory: Dyspnea, apnea, asphyxia.
Other: Decreased sweating, nasal stuffiness or congestion, sneezing, throat congestion, impotence, suppression of lactation.

4.9 Overdose

Mefenamic Acid

Symptoms: Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Mefenamic acid has a tendency to induce tonic-clonic (grand mal) convulsions in overdose. Gastrointestinal bleeding, hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.
Treatment: Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (5 to 10 times the usual dose). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

Dicyclomine Hydrochloride

Symptoms: Symptoms of dicyclomine overdose are headache, nausea, vomiting, blurred vision, dilated pupils, hot dry skin, dizziness, dryness of the mouth, difficulty in swallowing, and CNS stimulation. A curare-like action may occur (i.e., neuromuscular blockade leading to muscular weakness and possible paralysis).
Treatment: Treatment should consist of gastric lavage, emetics, and activated charcoal. It is not known whether dicyclomine is dialyzable. Sedatives (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

Mefenamic Acid

The mechanism of action of mefenamic acid is related to prostaglandin inhibition. Prostaglandins are implicated in a number of disease processes including inflammation, modulation of the pain response, dysmenorrhea, menorrhagia, and pyrexia.
Like all other NSAIDs, mefenamic acid inhibits the enzyme cyclooxygenase (COX) which is responsible for formation of prostaglandins (PGs). This results in a reduction in the rate of prostaglandin synthesis and reduced prostaglandin levels. Additionally, mefenamic acid also blocks the prostaglandin receptors to prevent the effects of preformed prostaglandins i.e., it

inhibits binding of PGE_2 to its receptors. Mefenamic acid therefore inhibits both, the synthesis and response to prostaglandins. Mefenamic acid acts centrally as well as peripherally. This dual site, double blockade mode of action of mefenamic acid is important in its clinical efficacy.

Dicyclomine Hydrochloride

Dicyclomine relieves smooth muscle spasm of the gastrointestinal, biliary and ureteric tracts. This action of dicyclomine is achieved via a dual mechanism:

1. A specific anticholinergic effect (antimuscarinic) at the acetylcholine-receptor sites with approximately $\frac{1}{8}^{th}$ the milligram potency of atropine.
2. A direct spasmolytic effect upon smooth muscles (musculotropic) of intestine, bile duct, ureters and uterus.

5.2 Pharmacodynamic Properties

Mefenamic Acid

Mefenamic acid belongs to the NSAID category which exhibit anti-inflammatory, analgesic, and antipyretic activities. Mefenamic acid has analgesic and antipyretic properties acting by both central and peripheral mechanisms. Mefenamic acid relives spasmodic pain as well as pain due to musculoskeletal disorders.

Dicyclomine Hydrochloride

Dicyclomine hydrochloride is an anti-spasmodic and anti-muscarinic agent. Dicyclomine hydrochloride relieves smooth muscle spasm of the GI tract and other smooth muscles such as uterus, ureters, and bile duct. Dicyclomine hydrochloride produces anticholinergic effects such as it reduces GI secretions and motility, inhibit the secretion of saliva and sweat, dilate the pupils, etc.

5.3 Pharmacokinetic Properties

Mefenamic Acid

Mefenamic acid is rapidly absorbed after oral administration. Peak plasma levels are attained in 2 to 4 hours. More than 90% of mefenamic acid is bound to plasma proteins, mainly albumin. Mefenamic acid is metabolized by cytochrome P450 enzyme [CYP2C9] to 3-hydroxymethyl mefenamic acid. Approximately 52% of a mefenamic acid dose is excreted into the urine and up to 20% of the dose is excreted by fecal route. The elimination half-life of mefenamic acid is approximately 2 hours. Because both renal and hepatic excretions are significant pathways of elimination, dosage adjustments in patients with renal or hepatic dysfunction may be necessary.

Dicyclomine Hydrochloride

Dicyclomine is rapidly absorbed after oral administration, reaching peak values within 60 to 90 minutes. Mean volume of distribution following a 20 mg oral dose is approximately 3.65 L/kg, suggesting extensive distribution in tissues. The metabolism of dicyclomine was not 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

Mefenamic Acid

Studies to evaluate the potential effects of the combination of mefenamic acid and dicyclomine on carcinogenicity, mutagenicity, or impairment of fertility have not been conducted.

Mefenamic acid does not have any known carcinogenic potential, and is not teratogenic in mice or rats. Delayed parturition occurs in rats. Large doses produce excitement, incoordination, depression, and convulsions in mice. Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities.

Dicyclomine Hydrochloride

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of dicyclomine. 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.

7. Description

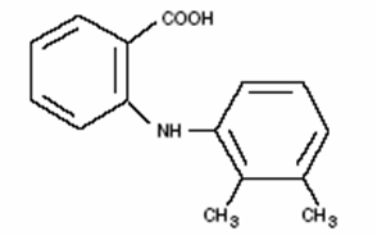
MEFTAL-SPAS Tablet are pale yellow, circular, flat, beveled, uncoated tablets with inscription of a circle and ‘MEFTAL-SPAS’ embossed on both sides.

MEFTAL-SPAS DS Tablets are pale yellow, capsule shaped biconvex, uncoated tablets with score line on one side and plain on other side.

MEFTAL-SPAS Tablet and MEFTAL-SPAS DS Tablets contain 250 mg / 500 mg of mefenamic acid and 10 mg / 20 mg of dicyclomine hydrochloride respectively for oral administration in adults and adolescents.

Mefenamic Acid

Mefenamic acid is a member of the fenamate group of non-steroidal anti- inflammatory drugs (NSAIDs). Mefenamic acid is a white to greyish-white, odorless, microcrystalline powder.
Chemical Name: N-2,3-xylylanthranilic acid.
Molecular Weight: 241.29 g/mol.
Molecular Formula: $C_{15}H_{15}NO_2$.
Structural Formula:



Dicyclomine Hydrochloride

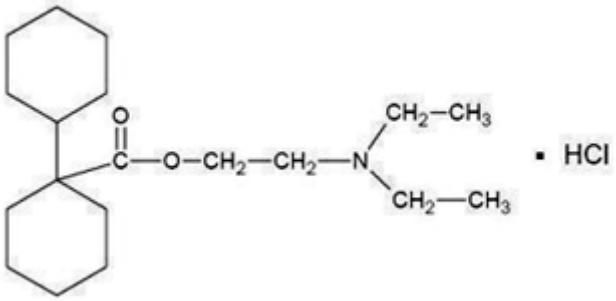
Dicyclomine is an antispasmodic agent with anticholinergic properties. Dicyclomine hydrochloride occurs as a fine, white, crystalline, practically odorless powder with a bitter taste. It is soluble in water, freely soluble in alcohol and chloroform, and very slightly soluble in ether.

Chemical Name: [bicyclohexyl]-1-carboxylic acid, 2-(diethylamino) ethyl ester, hydrochloride.

Molecular Weight: 345.95 g/mol.

Molecular Formula: C19H35NO2•HCl.

Structural Formula:



Inactive ingredients (excipients) of MEFTAL-SPAS Tablet contain Microcrystalline Cellulose, Maize Starch, Povidone K-30, Propylene Glycol, Colour Tartrazine, Purified Water, Sodium Starch Glycolate, Purified Talc, Colloidal Silicon Dioxide, and Magnesium Stearate.

Inactive ingredients (excipients) of MEFTAL-SPAS DS Tablet contain Microcrystalline Cellulose, Maize Starch, Povidone K-30, Propylene Glycol, Colour Tartrazine, Purified Water, Sodium Starch Glycolate, Purified Talc, Colloidal Silicon Dioxide, and Magnesium Stearate.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2 Shelf-life

36 months.

8.3 Packaging Information

10 tablets per strip.

8.4 Storage and Handling Instructions

Store protected from light and moisture at a temperature not exceeding 30°C.
Keep out of reach of children.

9. Patient Counseling Information

Administration Instructions

- Instruct patients to take prescribed dose as directed
- If pregnant or breast-feeding, ask a health professional before use. Instruct pregnant women not to take this medicine especially in the last 3 months of pregnancy as it may cause harm to the fetus and during labour (delivery) because it may delay the labour and increases risk of bleeding.
  Instruct breastfeeding women not to use this drug during lactation. If drug therapy is essential, breast-feeding must be discontinued during treatment period.
- Instruct users not to expose themselves with high temperature conditions as decreased sweating, fever and heat stroke can occur with this medicine (dicyclomine). If symptoms occur, the drug should be discontinued and contact doctor immediately.
- This drug may produce drowsiness or blurred vision. The patient should be warned not to engage in activities requiring mental alertness, such as operating machinery or driving vehicle while on therapy.

10. Details of Manufacturer

M/s. Blue Cross Laboratories Pvt. Ltd.,
L-17, Verna Industrial State, Verna,
Goa – 403 722, India.

11. Details of Permission or License Number with Date

DCG(I) NOC date: 26th June 2018.
Manufacturing License No.: 271.
Date of Product Permission for MEFTAL-SPAS Tablets: 30th November 1988.
Date of Product Permission for MEFTAL-SPAS DS Tablets: 28th November 1996.

12. Date of Revision

January 2021.