For the use of only a Registered Medical Practitioner or a Hospital or a Laboratory

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

Prescribing Information

1. Generic Name

Mefenamic Acid Dispersible Tablets
(Brand Name: MEFTAL®-P Tablets)

2. Qualitative and Quantitative Composition

Each Dispersible Uncoated Tablet Contains:
Mefenamic Acid IP …….. 100 mg.
Excipients ……. q.s.
Colour: Tartrazine

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Mefenamic acid 100 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

MEFTAL-P Dispersible Tablets are indicated for the symptomatic treatment of fever in children above 6 months of age.
Mefenamic acid is also useful for the relief of mild to moderate pain in children.

4.2Posology and Method of Administration

For oral administration in children.

Recommended dosage of mefenamic acid based on age group

- **2 to 4 years:** 100 mg three times daily.
- **5 to 8 years:** 150 mg three times daily.
- **9 to 12 years:** 200 mg three times daily.

Mefenamic acid dosage based on body weight: 4 to 6.5 mg/kg body weight every 8 hours, or 25 mg/kg/day in three divided doses, as needed.
Do not exceed the recommended dosage in children.
Or, as prescribed by the physician.

Directions for Reconstitution of the Dispersible Tablets

Dispersible Tablets should be reconstituted by the addition of an adequate amount of clean potable water (5 to 10 ml) immediately before use. Stir well until the tablet gets properly dispersed in the water and then swallow.

4.3Contraindications

MEFTAL-P Dispersible Tablets are contraindicated in the following:

- Known hypersensitivity to mefenamic acid or to any component of the formulation.
- Preexisting asthma and aspirin-sensitive asthma.
- Treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.
- Active ulceration or chronic inflammation of either the upper or lower gastrointestinal (GI) tract.
- Pre-existing renal disease.
- Last trimester of pregnancy.

4.4Special Warnings and Precautions for Use

Cardiovascular Thrombotic Events: Clinical trials of several 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 gastrointestinal (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.

4.5Drug Interactions

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.

ACE-Inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (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 C_{max} and AUC of mefenamic acid increasing by 125% and 36%, respectively.

4.6Use in Special Populations

Pregnant Women

Pregnancy Category C. There are no adequate or well controlled studies of mefenamic acid available in pregnant women. Congenital abnormalities have been reported in association with NSAID administration 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 labour 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 labour unless the potential benefit to the patient outweighs the potential risk to the fetus.

Lactating Women

Trace amounts of mefenamic acid may be present in breast milk and transmitted to the nursing infant. But, the risk to the infants seems to be limited. Mefenamic acid is generally compatible with breast feeding.

Paediatric Patients

Safety and effectiveness of mefenamic acid in paediatric patients below the age of 6 months has not been established. For dosage in children above 6 months, please refer ‘Posology and Method of Administration’ section.

Geriatric Patients

The elderly patients have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal (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). Elderly patients with normal renal function may be given the same dose as recommended for adults. 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

Mefenamic acid should not be administered to patients with preexisting renal disease or in patients with significantly impaired renal function.

4.7Effect 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. If affected, patients should not drive or operate machinery.

4.8Undesirable Effects

The most frequently reported side effects associated with mefenamic acid involve the gastrointestinal tract. Diarrhea occasionally occurs following the use of mefenamic acid.

Frequencies are not known for the following adverse reactions:

Gastrointestinal Disorders: The most commonly observed adverse events are gastrointestinal 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 gastrointestinal 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 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, hyponatraemia may occur.

Pyschiatric 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-Bilary 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, fixed drug eruption (FDE), 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. Hypothermia may occur, *albeit* rarely, in paediatric patients.
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.

4.9Overdose

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.

5. Pharmacological Properties

5.1 Mechanism of Action

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. 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 has analgesic and antipyretic properties acting by both central and peripheral mechanisms. This dual site, double blockade mode of action of mefenamic acid is important in its clinical efficacy.

5.2Pharmacodynamic Properties

Mefenamic acid belongs to the NSAID category which exhibit anti-inflammatory, analgesic, and antipyretic activities.

5.3Pharmacokinetic Properties

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.

6. Nonclinical Properties

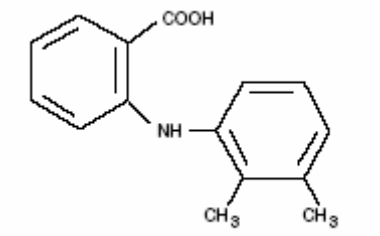
6.1 Animal Toxicology

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.

7. Description

MEFTAL-P Dispersible Tablets are Pale yellow coloured, circular, flat, beveled, uncoated tablets with score line on one side and plain on other side.
Each dispersible tablet of MEFTAL-P contains 100 mg of mefenamic acid for oral administration.

Mefenamic acid is a member of the fenamate group of NSAIDs. Mefenamic acid is a white to greyish-white, odorless, microcrystalline powder.
Molecular Weight: 241.29 g/mol.
Chemical Name: N-2,3-xylylanthranilic acid.
Molecular Formula: C15H15NO2.
Structural Formula:



Inactive ingredients (excipients) of MEFTAL-P Dispersible Tablet contains Microcrystalline Cellulose, Starch, Sodium Starch Glycollate, Saccharin Sodium, Polyvinylpyrrolidone K-30, Colour Tartrazine, Propylene Glycol, Sodium Lauryl Sulphate, Purified Water, Flavour Capsaroma Mango, Colloidal Silicon Dioxide & Magnesium Stearate.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

36 Months

8.3Packaging Information

Strip of 10 tablets.

8.4Storage 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

Instructions to patients/caregivers:

- NSAID medicines should be used exactly as prescribed, at the lowest dose possible, and for the shortest time needed. Patients should not exceed the recommended dose or duration of treatment.
- Pregnant women should consult their doctor before use of this medicine. Pregnant women are advised not to take MEFTAL-P Dispersible Tablets 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.
- This medicine should be strictly avoided in children below 6 months of age.
- Do not administer this medicine if patient had an asthma attack, urticaria/itching, or other allergic reaction with aspirin or any other NSAID medicine.
- Administer this medicine after food to reduce the stomach discomfort (heartburn).

10. Details of Manufacturer

Blue Cross Laboratories Pvt Ltd.

L – 17, Verna Industrial Estate, Verna, Goa – 403722.

11. Details of Permission or License Number with Date

Mfg. Lic. No. : 271 Date of FDA Product Permission: 27/05/1996

12. Date of Revision

June 2022.