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

Prescribing Information

1. Generic Name

Paracetamol and Mefenamic Acid Tablets

(Brand Name: MEFTAL-FORTE® Tablets)

Paracetamol: Box Warning About Its Liver Toxicity

Taking more than daily dose may cause serious liver damage or allergic reactions (e.g., swelling of the face, mouth and throat, difficulty in breathing, itching or rash). The risk of liver injury primarily occurs when patient take multiple products containing paracetamol/acetaminophen at one time and exceed the current maximum dose of 4,000 mg within a 24-hour period.

2. Qualitative and Quantitative Composition

Each uncoated tablet contains:
Paracetamol IP ……..… 325 mg.
Mefenamic Acid IP ……..… 500 mg.
Colour: Tartrazine.

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Paracetamol 325 mg with Mefenamic Acid 500 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

MEFTAL-FORTE Tablets are indicated for the symptomatic relief of mild to moderate pain in following conditions:

- Headache.
- Migraine.
- Dental pain.
- Post-operative pain.
- Post-partum pain.
- Pain associated with acute musculoskeletal disorders such as sprains and strains.
- Muscular and traumatic pain.
- Low back pain.

4.2 Posology and Method of Administration

For Oral Administration in Adults and Adolescents: 1 tablet of MEFTAL-FORTE to be administered three times daily.
Do not exceed the stated dose.

MEFTAL-FORTE Tablets should be taken preferably with or after food.
Or, as prescribed by the physician.

4.3 Contraindications

MEFTAL-FORTE Tablet is contraindicated in the following:

- Known or suspected hypersensitivity to paracetamol or to mefenamic acid or to any component of this formulation
- Pre-existing asthma and aspirin-sensitive asthma
- Active ulceration/bleeding or chronic inflammation of upper or lower gastrointestinal (GI) tract
- Pre-existing renal disease/obstructive uropathy
- Last trimester of pregnancy
- Treatment of peri-operative pain during coronary artery bypass graft (CABG) surgery

4.4 Special Warnings and Precautions for Use

Paracetamol

Hepatotoxicity: Significant overdose of paracetamol can lead to hepatotoxicity in some patients. Thus, do not exceed the recommended dose. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

Other Paracetamol-Containing Products: Do not take with any other paracetamol-containing products, so as to avoid the chances of overdose.

Renal and Hepatic Impairment: Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment.

Alcohol: Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive paracetamol 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 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 enzymes aspartate transaminase (AST) and alanine transaminase (ALT) 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 angiotensin converting enzyme (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 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 symptoms. 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.

Laboratory Test Abnormalities: 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 reagent tablet test, may result after mefenamic acid administration. If biliuria is suspected, other diagnostic procedures, such as the Harrison spot test, should be performed.

4.5 Drug Interactions

Paracetamol

Cholestyramine: The rate of absorption of paracetamol is reduced by cholestyramine. Therefore, cholestyramine should not be taken within one hour, if maximal analgesia is required.

Metoclopramide and Domperidone: The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.

Warfarin: The anti-coagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.
Chloramphenicol: Concurrent administration of paracetamol and chloramphenicol may markedly retard the elimination of chloramphenicol and thus, increases plasma concentration of chloramphenicol which leads to risk of its harmful effects. Monitoring of chloramphenicol plasma levels is recommended while combining paracetamol with chloramphenicol injection.
Alcohol, Anticonvulsants, and Isoniazid: Concomitant administration of alcohol, anticonvulsants, and isoniazid with paracetamol may increase risk of hepatotoxicity.

Mefenamic Acid

A number of compounds are inhibitors of cytochrome P450 2C9 (CYP2C9) enzymes. 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 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 higher 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 the 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 Hypoglycaemic Agents: NSAIDs may inhibit metabolism of sulfonylurea drugs, thereby prolongs half-life and increases risk of hypoglycaemia. 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 haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in human immunodeficiency virus positive [HIV(+)] haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

4.6 Use in Special Populations

Pregnant Women

Paracetamol: Pregnancy Category B; Mefenamic Acid: Pregnancy Category C. There are no adequate or well controlled studies of paracetamol with mefenamic acid combination therapy in pregnant women. Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage. Congenital abnormalities have been reported with use of NSAIDs in humans. NSAIDs are also known to produce effects on the

fetal cardiovascular system (i.e., risk of premature closure of the ductus arteriosus). Thus, MEFTAL-FORTE Tablets are contraindicated for use in the third trimester of pregnancy. When used during labour, the onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child. MEFTAL-FORTE Tablets should not be used during 1st and 2nd trimester of pregnancy or labour unless the potential benefit to the patient outweighs the possible risk to the fetus.

Lactating Women

Paracetamol is excreted in breast milk, but not in significant amounts. 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. Published clinical data does not contraindicate use of paracetamol while breast-feeding. Literature and clinical evidence also suggest that both, paracetamol and mefenamic acid are compatible with breast-feeding. Thus, if required, MEFTAL-FORTE Tablets can be administered in lactating women.

Paediatric Patients

MEFTAL-FORTE Tablets are not intended for use in children as there is no feasibility of dosage adjustments. Mefenamic acid is not recommended in children below 6 months of age. In recommended dosage, paracetamol is usually safe in children. It is advised that children under 12 years of age should use paediatric formulations of these drugs.

Geriatric Patients

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 with regard to use of mefenamic acid in the elderly population (> 65 years).
Elderly patients with normal renal function may be given the same dose as recommended for adults. Both, mefenamic acid and paracetamol are mainly excreted by the kidney, and the risk of adverse reactions to these drugs 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

Paracetamol is mainly excreted by renal route; therefore, it should be used with caution in patients with renal dysfunction. In cases of severe renal impairment (creatinine clearance ≤30 ml/min), longer dosing intervals and a reduced total daily dose of paracetamol is advised. Mefenamic acid and its metabolites are also primarily excreted by the kidney. Thus, risk of adverse reactions may be greater in patients with impaired renal function as accumulation of mefenamic acid metabolites may occur. Mefenamic acid should not be administered to patients with preexisting renal disease or in patients with significantly impaired renal function. MEFTAL-FORTE Tablets should be avoided in patients with severe renal impairment and it should be used with caution in patients with mild to moderate renal impairment.

Hepatic Impairment Patients

Caution should be exercised while administering paracetamol to patients with severe hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease. As hepatic metabolism is a significant pathway of mefenamic acid elimination, patients with acute and chronic hepatic disease may require reduced doses of mefenamic acid compared to patients with normal hepatic function. MEFTAL-FORTE Tablets are contraindicated in patients with severe hepatic impairment or severe active liver disease and it should be used with caution in patients with mild to moderate hepatic impairment.

4.7 Effect on Ability to Drive and Use Machines

No adverse effects known with paracetamol. Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs such as mefenamic acid. If affected, patients should not drive or operate machinery.

4.8 Undesirable Effects

MEFTAL-FORTE Tablets are generally well tolerated. Adverse effects are usually mild, infrequent, and transient in nature.

Paracetamol

Adverse effects of paracetamol are rare. However, hypersensitivity including skin rash and fixed drug eruption (FDE) may occur. There have been reports of blood dyscrasias including thrombocytopenic purpura, methaemoglobenemia and agranulocytosis, but these were not necessarily related to paracetamol. Overdosage with paracetamol can result in severe hepatotoxicity and sometimes acute renal tubular necrosis. If there is a pre-existing liver insufficiency, paracetamol can be hepatotoxic even in normal dosage. Increased levels of aspartate aminotransferase and hepatic transaminases may occur. Nausea, vomiting, abdominal pain, diarrhea, constipation, dyspepsia, dry mouth, heartburn have also been reported commonly with the use of paracetamol.

Mefenamic Acid

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

Frequencies are not known for the following adverse reactions:

GI Disorders: The most commonly observed adverse events are gastrointestinal in nature. Heartburn due to hyperacidity, 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 lesser 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, aggravated asthma, bronchospasm, or dyspnea; 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 and 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 and dyspnea have been reported.

Hepato-Bilary Disorders: Borderline elevations of one or more liver function tests and 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.

Laboratory Tests: 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.

4.9 Overdose

Paracetamol

Symptoms: Ingestion of 5 gram or more of paracetamol may lead to liver damage. Symptoms of paracetamol overdose in the first 24 hours are pallor, nausea, vomiting, anorexia and

abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, hemorrhage, hypoglycaemia, cerebral edema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, hematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Treatment: Immediate treatment is essential in the management of paracetamol overdose. Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine (FDA approved antidote) may be used up to 24 hours after ingestion of paracetamol. However, the maximum protective effect is obtained up to 8 hours post ingestion.

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.

5. Pharmacological Properties

5.1 Mechanism of Action

Paracetamol

Antipyretic Effect: Paracetamol produces antipyretic effect by acting centrally on the hypothalamic heat-regulation center to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating and heat loss. The central action involves inhibition of prostaglandin synthesis in the hypothalamus.

Analgesic Effect: The mechanism of analgesic action of paracetamol has not been fully determined. Paracetamol may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS).

Mefenamic Acid

The mechanism of action of mefenamic acid is related to prostaglandin inhibition. Prostaglandins (PGs) 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 prostaglandin E2 (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.

5.2 Pharmacodynamic Properties

Paracetamol

Paracetamol is centrally acting antipyretic and analgesic agent. Paracetamol has analgesic and antipyretic effects similar to those of aspirin and is useful in the treatment of mild to moderate pain and reduction of fever. Paracetamol has only weak anti-inflammatory effects.

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.

5.3 Pharmacokinetic Properties

Paracetamol

Paracetamol is readily absorbed from the GI tract with C_{max} occurring about 30 minutes to 2 hours after ingestion. Paracetamol is metabolized in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours. Plasma protein binding is negligible at usual therapeutic concentrations, but rises with increasing concentrations.

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.

6. Nonclinical Properties

6.1 Animal Toxicology

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

Paracetamol

Preclinical data reveal no special hazard for humans with paracetamol based on conventional studies of single and repeated dose toxicity, genotoxicity and carcinogenicity. Studies for the evaluation of toxicity to reproduction and development are not available.

Mefenamic Acid

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.

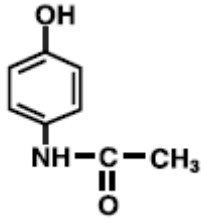
7. Description

MEFTAL-FORTE Tablets are pale yellow coloured, elongated, biconvex, uncoated, tablets with MEFTAL-FORTE engraved on one side and scored on other side.

Each tablet of MEFTAL-FORTE contains 325 mg of paracetamol and 500 mg of mefenamic acid for oral administration.

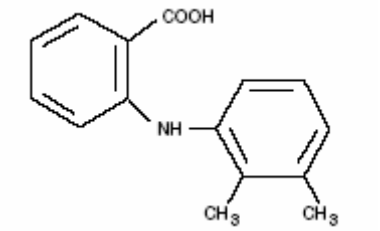
Paracetamol

Paracetamol, also called as acetaminophen, is a slightly bitter, white, odorless, crystalline powder. Paracetamol is a non-opiate, non-salicylate analgesic and antipyretic agent.
Chemical Name: 4'-hydroxyacetanilide.
Molecular Weight: 151.16 g/mol.
Molecular Formula: C8H9NO2.
Structural Formula:



Mefenamic Acid

Mefenamic acid is a member of the fenamate group of 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: C15H15NO2.
Structural Formula:



Inactive ingredients (excipients) of MEFTAL-FORTE Tablet contains Pregelatinized Starch, Polyvinyl Pyrrolidone K – 90, Polyvinyl Pyrrolidone K – 30, Propylene Glycol, Colour Tartrazine, Sodium Methyl Paraben, Sodium Propyl Paraben, Purified Water, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Magnesium Stearate, and Talcum.

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.
Keep out of reach of children.

9. Patient Counseling Information

Administration Instructions

Instruct patients to:

- Ensure the prescribed dose of MEFTAL-FORTE Tablet is taken as directed.
- If pregnant or breast-feeding, ask a healthcare professional before use. Instruct pregnant women not to take MEFTAL-FORTE 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.
- Not to use with any other drug containing paracetamol (prescription or over-the-counter - OTC). Users to ask a doctor or pharmacist, if they are not sure about presence of paracetamol in the drug taken for other illnesses.

10.Details of Manufacturer

M/s.Akums Drugs and Pharmaceuticals Ltd.,
21, Sector-6A, IIE, Ranipur,
Haridwar - 249 403 Uttarakhand, India.

11. Details of Permission or License Number with Date

DCG(I) NOC date: 13th October 2016.
Manufacturing License No. 31/UA/2013. Date of Product Permission - 3rd April 2017.

12. Date of Revision

February 2023.

Marketed by:
BLUE CROSS LABORATORIES PVT LTD.
A-12, M.I.D.C., NASHIK-422 010.
Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.