SUMMARY OF PRODUCT CHARACTERISTICS

1.1 Name of the finished pharmaceutical product : MEFTAL – 500 TABLETS

(Invented) name of the medicinal product :MEFENAMIC ACID TABLETS BP

1.2 **Strength :** Mefenamic Acid 500 mg / Tablet

1.3 **Pharmaceutical form :** Oral Solid (Uncoated Tablet)

2. Qualitative and Quantitative composition

Qualitative declaration :

Each Uncoated Tablet Contains :

Mefenamic Acid BP ..... 500 mg

2.1 Quantitative declaration :

Sr. No	Name of API	Grade	Label claim per Tab in mg	Overages (%)	Input Qty / Tab in mg
1.	Mefenamic Acid	BP	500 mg	--	500.00

3. Pharmaceutical form :

Off white capsule shaped, uncoated tablets with score line on one side & plain on the other side.

Packed in printed aluminium and amber coloured PVC blister .

4. Clinical particulars :

4.1 Therapeutic indications :

MEFTAL Tablets are indicated for:

- Relief of mild-to-moderate pain including headache, dental pain, postoperative and postpartum pain, and primary dysmenorrhoea.
- In musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis.
- In menorrhagia.

4.2 Posology and method of administration :

Adults: 500 mg three times daily or 500 mg as an initial dose followed by 250 mg every 6 hours as needed.

Mefenamic acid should not be given for longer than 7 days at a time.

Primary Dysmenorrhea: 500 mg of mefenamic acid as an initial dose followed by 250 mg every six hours, starting at onset of bleeding and associated symptoms. Treatment with mefenamic acid should not be necessary for more than 2 to 3 days.

Or, as prescribed by the physician.

4.3 Method of administration : By oral route

4.4 Contraindications :

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

4.5 Special warnings and precautions for use :

Cardiovascular Thrombotic Events: Clinical trials of several COX-2 selective and nonselective 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) 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 NSAISs 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.

4.6 Paediatric population

Not Applicable

4.7 Interaction with other medicinal products and other forms of interaction :

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 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 (n=6), ingestion of an antacid containing 1.7-gram of magnesium hydroxide with 500-mg of mefenamic acid increased the Cmax and AUC of mefenamic acid by 125% and 36%, respectively.

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.

4.8 Additional information on special populations :

Not Applicable

4.9 Paediatric population :

Not Applicable

4.10 Fertility, pregnancy and lactation :

Pregnancy

Pregnancy Category C. There are no adequate or well controlled studies in pregnant women. Congenital abnormalities have been reported in association with NSAID administration in human; 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 foetal cardiovascular system (risk of closure of the ductus arteriosus), use 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 should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the possible risk to the foetus.

Nursing Mothers

Trace amounts of mefenamic acid may be present in breast milk and transmitted to the nursing infant. Because of the potential for serious adverse reactions in

nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of mefenamic acid in pediatric patients below the age of 6 months has not been established. This formulation is not recommended for use in children as there is no feasibility of dosage adjustments. It is advised that children under 12 years of age should be given mefenamic acid suspension.

Geriatric Use

As with any NSAIDs, caution should be exercised while use of mefenamic acid in treating the elderly (65 years and older). This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug 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.

4.11 Effects 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.

4.12 Undesirable effects :

In patients taking mefenamic acid or other NSAIDs, the most frequently reported adverse experiences occurring in approximately 1-10% of patients are:

Gastrointestinal experiences including-abdominal pain, constipation, diarrhea, dyspepsia, flatulence, heartburn, nausea, vomiting, GI ulcers (gastric/duodenal), GI bleeding/perforation; abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes, tinnitus.

Additional adverse experiences reported occasionally and listed here by body system include:

Body as a whole: fever, infection, sepsis.

Cardiovascular system: congestive heart failure, hypertension, tachycardia,

syncope.

Digestive system: dry mouth, esophagitis, gastric/peptic ulcers, gastritis, gastrointestinal bleeding, glossitis, hematemesis, hepatitis, jaundice.

Hemic and lymphatic system: ecchymosis, eosinophilia, leukopenia, melena, purpura, rectal bleeding, stomatitis, thrombocytopenia.

Metabolic and nutritional: weight changes.

Nervous system: anxiety, asthenia, confusion, depression, dream abnormalities, drowsiness, insomnia, malaise, nervousness, paresthesia, somnolence, tremors, vertigo.

Respiratory system: asthma, dyspnea.

Skin and appendages: alopecia, photosensitivity, pruritus, sweat

Special senses: blurred vision.

Urogenital system: cystitis, dysuria, hematuria, interstitial nephritis, oliguria/polyuria, proteinuria, renal failure.

Other adverse reactions, which occur rarely are:

Body as a whole: anaphylactoid reactions, appetite changes.

Cardiovascular system: arrhythmia, hypotension, myocardial infarction, palpitations, vasculitis.

Digestive system: eructation, liver failure, pancreatitis.

Hemic and lymphatic system: agranulocytosis, hemolytic anemia, aplastic anemia, lymph- adenopathy, pancytopenia.

Metabolic and nutritional: hyperglycemia.

Nervous system: convulsions, coma, hallucinations, meningitis.

Respiratory: respiratory depression, pneumonia.

Skin and appendages: angioedema, toxic epidermal necrosis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, urticaria.

Special senses: conjunctivitis, hearing impairment.

4.13 Overdose :

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) convulsion in overdose. Gastrointestinal 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.

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

Mefenamic acid belongs to class of non-steroidal anti-inflammatory drugs (NSAIDs) that exhibit anti-inflammatory, analgesic, and antipyretic properties. Like NSAIDs in general, mefenamic acid acts by inhibiting the enzyme cyclooxygenase (COX) that is responsible for formation of prostaglandins.

5.1 Pharmacodynamic properties :

Pharmacotherapeutic group : Anti Inflammatory and Antipyretic

ATC Code : M01AG01

Mefenamic acid belonging to non-steroidal anti-inflammatory drugs (NSAIDs). Mefenamic acid exhibits anti-inflammatory, analgesic and antipyretic activities. The mechanism of action of mefenamic acid is related to prostaglandin inhibition. Like all other NSAIDs, mefenamic acid inhibits the enzyme, cyclooxygenase (COX) that is responsible for formation of prostaglandins. This results in a reduction in the rate of prostaglandin synthesis and reduced prostaglandin levels. However, additionally, mefenamic acid also blocks the prostaglandin receptors to prevent the effects of preformed prostaglandins.

Mefenamic acid therefore both inhibits the synthesis and response to prostaglandins. This double blockade may well be important in their mode of action.

5.2 Pharmacokinetic 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.

5.3 Preclinical safety data :

Preclinical safety data does not add anything of further significance to the prescriber.

6. Pharmaceutical particulars

6.1 List of excipients :

Microcrystalline Cellulose
Maize Starch
Povidone K – 90
Propylene Glycol
Sodium Lauryl Sulfate
Purified Water
Microcrystalline Cellulose D.C.
Colloidal Silicon Dioxide
Sodium Starch Glycolate
Croscarmellose Sodium
Magnesium Stearate

6.2 Incompatibilities :

None Known

6.3 Shelf life

48 Months

6.4 Special precautions for storage

Store below 30^0C in a dry place.

Protect from light.

6.5 Nature and contents of container :

Strip : Combi - Strip of 20 Tablets.

Carton : 5 Combi strip alongwith leaflet

Shipper : 80 outer cartons in 5 x 8 Style . Close the shipper and seal with BOPP tape in 'H' type packing on top and bottom side.

6.6 Special precautions for disposal and other handling

No special requirements

7. Marketing Authorisation Holder and Manufacturing Site Addresses

Blue Cross Laboratories Pvt Ltd.

L – 17, Verna Industrial Estate, Verna, GOA – 403 722.

8 Marketing Authorisation Number

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9. Date of First Registration/Renewal of the Registration

Renewal of the Registration

10. DATE OF REVISION OF THE TEXT

Not Applicable

11. DOSIMETRY (IF APPLICABLE)

Not Applicable

12. 1NSTRUCTIONS FOR PREPARATION OFRADIOPHARMACEUTICALS (IF APPLICABLE)

Not Applicable