1. Name of the medicinal Product

Mefenamic Acid Tablets BP (MEFLIN-500)

2. Qualitative and Quantitative Composition

2.1 Qualitative declaration

Mefenamic Acid BP

2.2 Quantitative declaration

Excipients with known effect

It contains tartrazine 0.500 mg

For full list of Excipients, see section 6.1.

3. Pharmaceutical Form

Solid Oral Dosage Form, Tablets

Distribution Category: POM

Yellow coloured, capsule shaped, uncoated tablets, plain on both sides.

4. Clinical Particulars

1. Therapeutic Indications

It is indicated for follow treatment. 1. As an anti-inflammatory analgesic for the symptomatic relief of rheumatoid arthritis (including Still's Disease), osteoarthritis, and pain including muscular, traumatic and dental pain, headaches of most aetiology, post-operative and post-partum pain. 2. Primary dysmenorrhoea. 3. Menorrhagia due to dysfunctional causes and presence of an IUD when other pelvic pathology has been ruled out.

2. Posology and Method of Administration

Method of administration: For oral administration. It should be taken preferably with or after food or as directed by physician. Do not exceed the stated dose.

Adults: 1 tablet (500 mg) three times daily. In menorrhagia to be administered on the first day of excessive bleeding and in dysmenorrhoea to be administered at the onset of menstrual pain continued according to the judgement of the physician.

Elderly (over 65 years): If an NSAID is considered necessary, the lowest effective dose and short duration should be used. The elderly may at increased risk of the serious consequences of adverse reactions.

Paediatric population (under12 years of age): It is not recommended.

3. Contraindications

Hypersensitivity to the active substance or any of individual component or excipients. It is also contraindicated in following conditions: Inflammatory bowel disease. History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active, or history of recurrent peptic ulcer/haemorrhage. Severe heart failure, hepatic failure and renal failure. Because the potential exists for cross-sensitivity to aspirin, ibuprofen, or other NSAIDs drugs, mefenamic acid must not be given to patients who have previously shown hypersensitivity reaction (e.g. asthma, bronchospasm, rhinitis, angioedema or urticaria) to these medicines. During the last trimester of pregnancy. Treatment of pain after coronary artery bypass graft surgery.

4. Special Warnings and Special Precautions for Use

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms

Patients should not take with alcohol it may increase the risk of especially (elderly patient's) gastrointestinal bleeding, ulceration and perforation which may be serious.

The elderly patient should be monitored regularly for GI bleeding during NSAID therapy. It should be used with caution if patients suffering from dehydration and renal disease. Non-oliguric renal failure and proctocolitis mainly in elderly patients who have not discontinued mefenamic acid after the development of diarrhoea.

Respiratory disorders: Caution is required if administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs to precipitate bronchospasm in such patients.

Cardiovascular and cerebrovascular effects: It should be used with caution in patients with a history of cardiac failure, left ventricular dysfunction, hypertension, ischaemic heart disease, peripheral arterial disease, cerebrovascular disease, in patients with oedema for any other reason, and in patients with other risk factors for cardiovascular events.

Cardiovascular, renal and hepatic impairment: use of NSAID may cause a dose dependant reduce in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients.

Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be serious. Smoking and alcohol use are added risk factors. It should be administered with caution and under close supervision in patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease), due to a risk of worsening of the disease. In patients with systemic lupus erythematosus and mixed connective tissue disorders there may be an increased risk of aseptic meningitis. Serious skin reactions, including exfoliative dermatitis, syndromes and Stevens-Johnson syndrome and toxic epidermal necrolysis may have been reported very rarely.

The use of mefenamic acid may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, avoid use of mefenamic acid should be considered. In dysmenorrhoea and menorrhagia lack of response should alert the physician to investigate other causes. Patients should be caution exercised when treating patients suffering from epilepsy.

Pregnancy: It should not be taken during pregnancy or avoiding them unless the potential benefit outweighs the risk.

Lactation: It is present in breast milk and transmitted to the nursing infant. Therefore, mefenamic acid should not be taken by nursing mothers.

Excipients with known effect: This product contain azo colouring agent: tartrazine; it may cause allergic reactions.

5. Interaction with other medicinal products and other forms of interaction

Concurrent therapy with other plasma protein binding drugs may necessitate a modification in dosage.

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4). Concurrent administration of mefenamic acid with oral anti-coagulant drugs requires careful prothrombin time monitoring.

It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.

Lithium: A reduction in renal lithium clearance and elevation of plasma lithium levels. Patients should be observed carefully for signs of lithium toxicity.

The following interactions have been reported with NSAIDs but have not necessarily been associated with Ponstan Forte Tablets:

Other analgesics including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects

Antidepressants: Selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding.

Anti-hypertensive and diuretics: A reduction in antihypertensive and diuretic effect has been observed. Diuretics can increase the nephrotoxicity of NSAIDs.

ACE inhibitors and angiotensin-II-receptor antagonists: A reduction in antihypertensive effect and an increased risk of renal impairment especially in elderly patients. Patients should be adequately hydrated, and the renal function assessed in the beginning and during concomitant therapy.

Aminoglycosides: Reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.
Anti-platelet agents: Increased risk of gastrointestinal ulceration or bleeding.

Acetylsalicylic Acid: Experimental data implies that mefenamic acid interferes with the anti-platelet effect of low-dose aspirin when given concomitantly, and thus may interfere with aspirin's prophylactic treatment of cardiovascular disease. However, the limitations of this experimental data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular mefenamic acid use.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels.

Ciclosporin: The risk of nephrotoxicity of ciclosporin may be increased with NSAIDs.

Corticosteroids: Concomitant use may increase the risk of gastrointestinal ulceration or bleeding.

Oral hypoglycaemic agents: Inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.

Methotrexate: Elimination of the drug can be reduced, resulting in increased plasma levels.

Mifepristone: NSAIDs should not be taken for 8-12 days after mifepristone administration, NSAIDs can reduce the effects of mifepristone.

Probenecid: Reduction in metabolism and elimination of NSAIDs and metabolites.
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: Possible increased risk of nephrotoxicity when NSAIDS are given with tacrolimus.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemaophiliacs receiving concurrent treatment with zidovudine and ibuprofen**.**

4.6 Pregnancy and Lactation

Pregnancy: It should not be taken during pregnancy or avoiding them unless the potential benefit outweighs the risk.

Lactation: It is present in breast milk and transmitted to the nursing infant. Therefore, mefenamic acid should not be taken by nursing mothers.

4.7 Effects on ability to Drive and use Machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances

are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

8. Undesirable Effects

Blood and the lymphatic system disorders: Haemolytic anaemia, hypoplasia bone marrow, haematocrit decreased, thrombocytopenic purpura, leukopenia with a risk of infection, sepsis, and disseminated intravascular coagulation. Agranulocytosis, aplastic anaemia, eosinophilia, neutropenia, thrombocytopenia. reversible when mefenamic acid is stopped.

Immune system disorders: Hypersensitivity reactions following treatment with NSAIDs. (a) non-specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm, or dyspnoea or (c) assorted skin disorders including rashes of various types, pruritus, urticaria, purpura, angioedema, and more rarely exfoliative or bullous dermatoses.

Metabolism and nutrition disorders: Glucose intolerance in diabetic patients, hyponatraemia. **Psychiatric disorders**: Confusion, depression, hallucinations, **Nervous system disorders:** Optic neuritis, headaches, paraesthesia, dizziness, reports of aseptic meningitis, with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation, convulsions, insomnia.

Eye disorders: Eye irritation, reversible loss of colour vision, blurred vision. Ear and labyrinth disorders: tinnitus, vertigo.

Cardiac / vascular disorders: Oedema, hypertension and cardiac failure in association with NSAID treatment.

Respiratory, thoracic and mediastinal disorders: Asthma, dyspnoea.

Gastrointestinal disorders: The most common peptic ulcers, perforation or GI bleeding may occur. Vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastrointestinal ulceration or bleeding GI events are in elderly. Anorexia, colitis, enterocolitis, gastric ulceration with or without haemorrhage, pancreatitis, steatorrhea. Hepatobiliary disorders: liver function tests, cholestatic jaundice. Mild hepatotoxicity, hepatitis, hepatorenal syndrome. Skin and subcutaneous tissue disorders: Angioedema, laryngeal oedema, erythema multiforme, face oedema, bullous reactions including Lyell's syndrome and Stevens-Johnson syndrome, perspiration, rash, pruritus and urticaria.

Renal and urinary disorders: Allergic glomerulonephritis, acute interstitial nephritis, dysuria, haematuria, nephrotic syndrome, non-oliguric renal failure, proteinuria, renal failure. General disorders fatigue, malaise, multi-organ failure. Investigate certain tests for bile in the urine of patients receiving treatment mefenamic acid to be due to the presence of the drug and its metabolites and not to the presence of bile.

<u>Reporting of suspected adverse reactions</u>

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the TMDA ADR reporting tool; website: https:// imis.tmda.go.tz/arrt or search for TMDA Adverse Reactions Reporting Tool in the Google Play Store;

9. Overdose

It is important that the recommended dose is not exceeded and the regime adhered to since some reports have involved daily dosages under 3g.

Symptoms: include headache, nausea, vomiting epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, tinnitus, fainting, occasionally and convulsions. It has a tendency to induce tonic-clonic

convulsions in overdose. In cases of significant poisoning acute renal failure and liver damage are possible.

Management: Patients should be treated symptomatically as required. Patients should be observed for at least four hours after ingestion of overdose. Within one hour of ingestion of overdose, amount activated charcoal and alternatively, in adult's gastric lavage should be considered. Good urine output should be ensured. Renal and liver function should be closely monitored. Frequent or prolonged convulsions should be treated with intravenous diazepam. Haemodialysis is of little value since mefenamic acid and its metabolites are firmly bound to plasma proteins.

5. Pharmacological Properties

1. Pharmacodynamics Properties

Pharmacotherapeutic Group: Non-steroidal anti-inflammatory agent and anti-rheumatic products, fenamates
ATC Code: M01AG01
It has a non-steroidal anti-inflammatory agent with analgesic properties, and a demonstrable antipyretic effect. It has been shown to inhibit prostaglandin activity. Reversibly inhibits cyclooxygenase-1 and 2 enzymes, which decreased form of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties. Other proposed mechanisms not fully elucidated, include inhibiting chemotaxis, altering lymphocyte activity, inhibiting neutrophil aggregation/ activation, and decreasing pro-inflammatory cytokine levels. Paracetamol inhibits the synthesis of prostaglandins in the central nervous system and peripherally blocks pain impulse generation; also produces antipyresis effect from inhibition of hypothalamic heat-regulating center.

2. Pharmacokinetic Properties

Absorption: It is absorbed from the gastro intestinal tract. Peak levels of 10 mg/l occur two hours after the administration of a 1g oral dose to adults.

Distribution: It has been reported as being greater than 90% bound to albumin. Apparent volume of distribution is 1.06 l/kg.

Biotransformation: It is predominantly metabolised by cytochrome P450 enzyme CYP2C9 in the liver, first to a 3 hydroxymethyl derivative (metabolite I) and then a 3-carboxyl derivative (metabolite II). Both metabolites undergo secondary conjugation to form glucuronides. Therefore, in patients who are known or suspected to be poor CYP2C9 metabolisers based on previous history/experience with other CYP2C9 substrates, it should be administered with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Elimination: 54% of a dose is recovered from the urine, 6% as mefenamic acid, 25% as metabolite I and 21% as metabolite II. Assay of stools over a 3-day period accounted for 10-20 % of the dose chiefly as unconjugated metabolite II. The plasma levels of unconjugated mefenamic acid decline with a half-life of approximately two hours.

3. Preclinical Safety Data

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

6. Pharmaceutical Particulars

1. List of Excipients

Microcrystalline Cellulose BP (PH 102)
Maize starch BP
Colour tartrazine (supra) IHS
Purified Talc BP
Croscarmellose Sodium USP-NF
Magnesium Stearate BP
Crospovidone (Polyplasdone) USP-NF
Colloidal Anhydrous Silica (Aerosil)SSBP

Purified water BP

2. Incompatibilities
Not applicable.

3. Shelf Life
36 months

4. Special Precautions for Storage
Do not store above 30°C. Protect from light.

5. Nature and Contents of Container
10 Tablets are packed in Alu-PVC pack; such 10 Blister are packed in a printed carton with packing insert.

6. Special precaution for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder
Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.

8. Marketing Authorization Number
TAN 22 HM 0399

9. Date of First <Registration> / Renewal of The <Registration>
21/09/2022

10. **Date of Revision of the Text**
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