Summary Product Characteristic for Pharmaceutical Product

1. Name of the medicinal product

Pause MF

2. Qualitative and quantitative composition

Each tablet contains Tranexamic acid 500mg and Mefenamic Acid 250mg

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

A Yellow coloured film coated oval shaped tablet.

4. Clinical particulars

4.1 Therapeutic indications

PAUSE-MF is indicated for the treatment of primary dysmenorrhoea and relief of mild to moderate pain associated with menorrhagia in women.

4.2 Posology and method of administration

Posology
One tablets to be taken three times daily.

Method of administration
Route of administration: Oral

4.3 Contraindications

- Hypersensitivity to the active substance or any of the excipients listed in section 6.1. - Severe renal impairment because of risk of accumulation, - Active thromboembolic disease.
- History of venous or arterial thrombosis
- Fibrinolytic conditions following consumption coagulopathy
- History of convulsions
- Inflammatory bowel disease
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Severe heart failure and hepatic failure.
- Because the potential exists for cross-sensitivity to aspirin, ibuprofen, or other non-steroidal anti-inflammatory drugs, this product 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 (CABG) surgery.

4.4 Special warnings and precautions for use

In case of haematuria of renal origin (especially in haemophilia), there is a risk of mechanical anuria due to formation of a ureteral clot.
In the long-term treatment of patients with hereditary angioneurotic oedema, regular eye examinations (e.g. visual acuity, slit lamp, intraocular pressure, visual fields) and liver function tests should be performed.
Patients with irregular menstrual bleeding should not use Tranexamic acid until the cause of irregular bleeding has been established. If menstrual bleeding is not adequately reduced by Tranexamic acid, an alternative treatment should be considered.
Tranexamic acid should be administered with care in patients receiving oral contraceptives because of the increased risk of thrombosis.
Patients with a previous thromboembolic event and a family history of thromboembolic disease (patients with thrombophilia) should use Tranexamic acid only if there is a strong medical indication and under strict medical supervision.
The blood levels are increased in patients with renal insufficiency. Therefore, a dose reduction is recommended.
The use of tranexamic acid in cases of increased fibrinolysis due to disseminated intravascular coagulation is not recommended.
Patients who experience visual disturbance should be withdrawn from treatment.
Clinical experience with Tranexamic acid in menorrhagic children under 15 years of age is not available.
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.
Patients on prolonged therapy should be kept under regular surveillance with particular attention to liver dysfunction, rash, blood dyscrasias or development of diarrhoea. Appearance of any of these symptoms should be regarded as an indication to stop therapy immediately.

Use with concomitant NSAIDs including cyclooxygenase 2 specific inhibitors.
Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of 'Medication Overuse Headache' should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.
Precaution should be taken in patients suffering from dehydration and renal disease, particularly the elderly.

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

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

Cardiovascular, Renal and Hepatic impairment: The administration of an NSAID may cause a dose dependant reduction 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.

Cardiovascular and cerebrovascular effects: Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.
Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for mefenamic acid.
Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with mefenamic acid after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

As NSAIDs can interfere with platelet function, they should be used in caution in patients with intracranial haemorrhage and bleeding diathesis.

Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events. Smoking and alcohol use are added risk factors.
The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly.
Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for patients at risk of GI bleeding such as the elderly, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk.
Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.
Caution should be advised in patients receiving concomitant medications which could increase the risk of gastrotoxicity or bleeding such as corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors or anti-platelet agents such as aspirin.
When GI bleeding or ulceration occurs in patients receiving mefenamic acid the treatment should be withdrawn.

SLE and mixed connective tissue disease: In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis.

Skin reactions: Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported in association with use of NSAIDs. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Mefenamic acid should be stopped at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

Female fertility: 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, withdrawal of mefenamic acid should be considered.

In dysmenorrhoea and menorrhagia lack of response should alert the physician to investigate other causes.

Epilepsy: Caution should be exercised when treating patients suffering from epilepsy.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
In patients who are known or suspected to be poor CYP2C9 metabolisers based on previous history/experience with other CYP2C9 substrates, mefenamic acid should be administered with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.
Cases of convulsions have been reported in association with tranexamic acid treatment. In cardiac surgery, most of these cases were reported following intravenous (i.v.) injection of tranexamic acid in high doses.

4.5 Interaction with other medicinal products and other forms of interaction

Tranexamic acid will counteract the thrombolytic effect of fibrinolytic preparations.
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. 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 mefenamic acid:

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.

Antihypertensives 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 antiplatelet 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 halflife 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 Fertility, pregnancy and lactation

Pregnancy

Congenital abnormalities have been reported in association with NSAID administration in man; 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 potential risk to the foetus.
Although there is no evidence from animal studies of a teratogenic effect, the usual caution with use of drugs in pregnancy should be observed.
Tranexamic acid crosses the placenta.

Breast-feeding

Tranexamic acid passes into breast milk to a concentration of approximately one hundredth of the concentration in the maternal blood. An antifibrinolytic effect in the infant is unlikely.
Trace amounts of mefenamic acid may be present in breast milk and transmitted to the nursing infant.
Therefore, Pause MF 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.

4.8 Undesirable effects

The most frequently reported side effects associated with mefenamic acid involve the gastrointestinal tract.
Diarrhoea occasionally occurs following the use of mefenamic acid. Although this may occur soon after starting treatment, it may also occur after several months of continuous use. The diarrhoea has been investigated in some patients who have continued this drug in spite of its continued presence. These patients were found to have associated proctocolitis. If diarrhoea does develop the drug should be withdrawn immediately and this patient should not receive mefenamic acid again.

Frequencies are not known for the following adverse reactions:

Blood and the lymphatic system disorders
Haemolytic anaemia*, anaemia, hypoplasia bone marrow, haematocrit decreased, thrombocytopenic purpura, temporary lowering of the white blood cell count (leukopenia) with a risk of infection, sepsis, and disseminated intravascular coagulation.
Agranulocytosis, aplastic anaemia, eosinophilia, neutropenia, pancytopenia, thrombocytopenia.
*Reversible when mefenamic acid is stopped.

Immune system disorders
Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (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 (including epidermal necrolysis and erythema multiforme).

Metabolism and nutritional disorders
Glucose intolerance in diabetic patients, hyponatraemia.

Psychiatric disorders
Confusion, depression, hallucinations, nervousness.

Nervous system disorders
Optic neuritis, headaches, paraesthesia, 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. Blurred vision, convulsions, insomnia. Convulsions particularly in cases of misuse.

Eye disorders
Eye irritation, reversible loss of colour vision, visual disturbances, colour vision disturbances, retinal/artery occlusion.

Ear and labyrinth disorders
Ear pain, tinnitus, vertigo.

Cardiac / Vascular disorders
Oedema, 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 (for example myocardial infarction or stroke).
Palpitations, Hypotension.
Thromboembolic events, Arterial or venous thrombosis at any sites.

Respiratory, thoracic and mediastinal disorders
Asthma, dyspnoea.

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, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melena, haematemesis, 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 haemorrhage, pancreatitis, steatorrhea.

Hepato-bilary disorders
Borderline elevations of one or more 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 (toxic epidermal necrolysis) and Stevens-Johnson syndrome, perspiration, rash, photosensitivity reaction, pruritus and urticaria. Allergic skin reactions.

Renal and urinary disorders
Allergic glomerulonephritis, acute interstitial nephritis, dysuria, haematuria, nephrotic syndrome, non-oliguric renal failure (particularly in dehydration), proteinuria, renal failure including renal papillary necrosis.

General disorders
Fatigue, malaise, multi-organ failure, pyrexia.

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.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Tranexamic acid:
Signs and symptoms may include nausea, vomiting, orthostatic symptoms and/or hypotension, dizziness, headache and convulsions. Initiate vomiting, then stomach lavage, and charcoal therapy. Maintain a high fluid intake to promote renal excretion. There is a risk of thrombosis in predisposed individuals. Anticoagulant treatment should be considered.

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

(a) Symptoms

Symptoms include headache, nausea, vomiting epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, tinnitus, fainting, occasionally convulsions [Mefenamic acid has a tendency to induce tonic-clonic (grand mal) convulsions in overdose]. In cases of significant poisoning acute renal failure and liver damage are possible.

(b) Therapeutic measure

Patients should be treated symptomatically as required

Within one hour of ingestion of a potentially toxic amount activated charcoal should be considered. Alternatively, in adult's gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Good urine output should be ensured

Renal and liver function should be closely monitored.

Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

Frequent or prolonged convulsions should be treated with intravenous diazepam.

Other measures may be indicated by the patient's clinical condition.

Haemodialysis is of little value since mefenamic acid and its metabolites are firmly bound to plasma proteins.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Tranexamic acid is an antifibrinolytic compound which is a potent competitive inhibitor of the activation of plasminogen to plasmin. At much higher concentrations it is a noncompetitive inhibitor of plasmin. The inhibitory effect of tranexamic acid in plasminogen activation by urokinase has been reported to be 6-100 times and by streptokinase 6-40 times greater than that of aminocaproic acid. The antifibrinolytic activity of tranexamic acid is approximately ten times greater than that of aminocaproic acid.

Mefenamic acid is a non-steroidal anti-inflammatory drug (NSAID) with anti- inflammatory, analgesic and antipyretic properties.

Its anti-inflammatory effect was first established in the UV erythema model of inflammation. Further studies included inhibition of granulation tissue growth into subcutaneous cotton pellets in rats and carrageenin induced rat paw oedema tests.

Antipyretic activity was demonstrated in yeast-induced pyresis in rats. In this model its antipyretic activity was roughly equal to that of phenylbutazone and flufenamic acid, but less than that of indomethacin.
Analgesic activity was demonstrated in tests involving pain sensitivity of rats paws inflamed by brewer's yeast. Mefenamic acid was less potent than flufenamic acid in this model.
Prostaglandins are implicated in a number of disease processes including inflammation, modulation of the pain response, dysmenorrhoea, menorrhagia and pyrexia.
In common with most NSAIDs mefenamic acid inhibits the action of prostaglandin synthetase (cyclooxygenase). This results in a reduction in the rate of prostaglandin synthesis and reduced prostaglandin levels.
The anti-inflammatory activity of NSAIDs in the rat paw oedema test has been correlated with their ability to inhibit prostaglandin synthetase. When mefenamic acid is ranked in both these tests it falls between indomethacin and phenylbutazone and it is probable that inhibition of prostaglandin synthesis contributes to the pharmacological activity and clinical efficacy of mefenamic acid.
There is also considerable evidence that the fenamates inhibit the action of prostaglandins after they have been formed. They therefore both inhibit the synthesis and response to prostaglandins. This double blockade may well be important in their mode of action.

5.2 Pharmacokinetic properties

Tranexamic acid

Absorption
Peak plasma Tranexamic acid concentration is obtained immediately after intravenous administration (500mg). Then concentration decreases until the 6th hour. Elimination halflife is about 3 hours.

Distribution
Tranexamic acid administered parenterally is distributed in a two compartment model. Tranexamic acid is delivered in the cell compartment and the cerebrospinal fluid with delay. The distribution volume is about 33% of the body mass.
Tranexamic acid crosses the placenta, and may reach one hundredth of the serum peak concentration in the milk of lactating women.

Elimination
Tranexamic acid is excreted in urine as unchanged compound. 90% of the administered dose is excreted by the kidney in the twelve first hours after administration (glomerular excretion without tubular reabsorption).
Following oral administration, 1.13% and 39% of the administered dose were recovered after 3 and 24 hours respectively.
Plasma concentrations are increased in patients with renal insufficiency.

Mefenamic acid

Absorption and Distribution
Mefenamic acid 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.

Metabolism
Mefenamic acid 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, mefenamic acid should be administered with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Elimination
Fifty-two percent 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 1020 % of the dose chiefly as unconjugated metabolite II.
The plasma levels of unconjugated mefenamic acid decline with a half-life of approximately two hours.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet Core:
Microcrystalline Cellulose [pH101]
Sodium Starch Glycolate [Primogel]
Povidone [PVP K-30]
Starch
Purified water
Talc
Colloidal silicon Dioxide
Magnesium Stearate
Lake of Quinoline yellow

Coat (Opadry White)
Hypromellose
Titanium dioxide
Macrogol/PEG 6000
Purified Water

6.2 Incompatibilities

None of the In-active ingredients of the formulation have been known to exhibit incompatibility with the Active ingredient.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store in a dry place, below 30°C. Protect from light.

6.5 Nature and contents of container

10 tablets are packed in a blister pack [Printed Aluminium foil /PVC foil].
3 such blister is packed in a Printed carton along with a Pack Insert

6.6 Special precautions for disposal and other handling

Keep away from the reach of children.

7. Marketing authorisation holder and manufacturing site addresses

Marketing authorisation holder

Emcure Pharmaceuticals Limited
T – 184, M.I.D.C.,
Bhosari, Pune – 411026, India.

Manufacturing Site Address

Emcure Pharmaceuticals Limited
Lane No.3, Phase-II, SIDCO Industrial Complex,
Bari-Brahmana, Jammu – 181 133, India.

8. Marketing authorisation number(s)

H2024/CTD8230/18092

9. Date of first authorisation/renewal of the authorisation

Date of first authorization: 09-Feb.2024

10. Date of revision of the text

Nov-2024