SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Mefenamic Acid 250 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg Mefenamic Acid PhEur.
Also contains lactose, for a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Capsules for oral use.

Appearance: Hard gelatin capsule with a blue cap and a brown body, printed with PV and the code " M250."

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mefenamic acid is a non-steroidal anti-inflammatory agent with analgesic properties, and a demonstrable antipyretic effect. It has been shown to inhibit prostaglandin activity.

Indications
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; pyrexia in children.
2. Primary dysmenorrhoea.
3. Menorrhagia due to dysfunctional causes and presence of an IUD when other pelvic pathology has been ruled out.

4.2 Posology and method of administration

Adults: 2 capsules (500 mg) three times daily, to be taken with or after food

In menorrhagia to be administered on the first day of excessive bleeding and continued according to the judgement of the physician.

In dysmenorrhoea to be administered at the onset of menstrual pain and continued according to the judgement of the physician.

Elderly (over 65 years): As for adults. Whilst no pharmacokinetic or clinical studies specific to the elderly have been undertaken, it has been used at normal dosage in trials which include many elderly patients.

However, it should be used with caution in elderly patients suffering from dehydration and renal failure. Non-oliguric renal failure and proctocolitis have been reported mainly in elderly patients who have not discontinued mefenamic acid after the development of diarrhoea.

The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest dose should be used and for the shortest possible duration. The patient should be monitored regularly for gastro-intestinal bleeding during NSAID therapy.

Children (under 12 years): Not recommended.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms. (see section 4.4). The patient should be monitored regularly for gastrointestinal bleeding during NSAID therapy

Administration: Oral, the capsules should be swallowed with a drink of water. To be taken preferably with or after food.

4.3 Contraindications

Hypersensitivity to Mefenamic acid or any of the other ingredients.

Because the potential exists for cross-sensitivity to aspirin, ibuprofen or other non-steroidal anti-inflammatory drugs, mefenamic acid should not be given to patients who have previously shown hypersensitivity reactions as these drugs induce symptoms of asthma, bronchospasm, allergic rhinitis, angioedema or urticaria.

Mefenamic acid is also contra-indicated in patients with inflammatory bowel disease (eg ulcerative colitis, Crohn’s disease), intestinal ulceration and history of upper 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).

Use with concomitant NSAIDs including cyclo oxygenase 2 specific inhibitors (See section 4.5 Interactions).

Severe heart failure, hepatic failure and renal failure (see section 4.4).

During the last trimester of pregnancy (see section 4.6).

Treatment of pain after coronary artery bypass graft (CABG) surgery.

4.4 Special warnings and precautions for use

In all patients:
Undesirable effects may be minimised by using the minimum effective dose for the shortest possible duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

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 (see section 4.8).

Use with concomitant NSAIDs including cyclooxygenase 2 selective inhibitors (see section 4.5).

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 (See section 4.2-Posology and administration).

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

Cardiovascular, Renal and Hepatic Impairment:
The administration of NSAIDs may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at great risk of this reaction is those with impaired renal function, cardiac impairment, liver

dysfunction, those taking diuretics and elderly. Renal function should be monitored in these patients (See also section 4.3-Contraindication)

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 and 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 (see section 4.3), and in the elderly These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (eg misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5)

Patients with a history of GI toxicity, particular 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 gastroxicity or bleeding, such as Corticosteroids, or anticoagulant such as warfarin, selective serotonin reuptake inhibitors or anti-platelet agents such as aspirin (See section4.5 Interactions).

When GI bleeding or ulceration occurs in patients receiving mefenamic acid, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn‘s disease) as these conditions may be exacerbated (See section 4.8 –Undesirable effects.).

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 the 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 the patient should not receive mefenamic acid again.

SLE and mixed connective tissue disease:
In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be increased risk of aseptic meningitis (See section 4.8 – Undesirable effects).

Skin reactions:
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk for 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 discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Blood dyscrasias:
Blood dyscrasias have been reported in association with mefenamic acid. Blood studies should be carried out during long term administration and the appearance of any dyscrasia is an indication to discontinue therapy.

Liver function tests:
Borderline elevations of one or more liver function tests may occur in some patients receiving mefenamic acid. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should have their therapy discontinued. Patients on prolonged therapy should be kept under surveillance with particular attention to the possibility of liver dysfunction.

Female fertility:
The use of mefenamic acid may impair female fertility and is not recommended in woman attempting to conceive. In woman who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of mefenamic acid should be considered.

Precaution should be taken in patients suffering from dehydration.

Gynaecological:

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.

Metabolic disorders:
Patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Each capsule contains 450 micrograms of sodium.

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 (see section 5.2)

4.5 Interaction with other medicinal products and other forms of interaction

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

Care should be taken in patients treated with any of the following drugs as interactions have been reported in some patients.

Anticoagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin see section 4.4 –Special warning and precautions for use). 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.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).

Anti-hypertensives: Reduced anti-hypertensive effect.

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.

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

Ciclosporin: Increased risk of nephrotoxicity with NSAIDs.

Corticosteroids: Increased risk of gastro-intestinal bleeding (see section 4.4-special warning and precaution for use).

Diuretics: Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

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

Lithium: Decreased elimination of lithium and elevation of plasma lithium levels. Patients should be observed carefully for signs of lithium toxicity.

Methotrexate: Decreased elimination of methotrexate.

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

Other analgesics including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk adverse effects (see section 4.3-Contraindication).

Quinoline antibiotics: Animal data indicate 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.

Probenecid: Reduction in metabolism and elimination of NSAIDs and metabolites.

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 (+) haemophiliacs receiving concurrent treatment with zidovudine.

4.6 Pregnancy, fertility and lactation

Pregnancy:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately

1.5 %. The risk is believed to increase with dose and duration of therapy. Congenital abnormalities have been reported in association with NSAIDs administration in man; however, these are low in frequency and do not appear to follow any discernible pattern.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

In view of the known effects of NSAIDs on the foetal cardiovascular system use in the last trimester of pregnancy in contraindicated.

The onset of labour may be delayed and the duration increased with an increase bleeding tendency in both mother and child (See section4.3 Contraindications). NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patients outweigh the potential risk to the foetus.

Lactation:
In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding. See section 4.4 Special warnings and precautions for use, regarding female fertility.

4.7 Effects on ability to drive and use machines

Dizziness, drowsiness, visual disturbances or headaches are possible undesirable effects after taking NSAIDs, if affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Gastro-intestinal: The most commonly observed adverse events are gastro-intestinal in nature. Peptic ulcer, perforation or GI bleeding, sometimes fatal, particularly in the elderly may occur (see section4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemsis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (See section4.4-) have been reported following administration. Pancreatitis has been reported. 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.

Diarrhoea occasionally occurs following the use of mefenamic acid. Although diarrhoea 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.

Colitis, enterocolitis, gastric ulceration with or without haemorrhage, steatorrhea, anorexia have been reported.

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, pruritis, urticaria, purpura, angioedema and, less commonly exfoliative or bullous dermatoses (including epidermal necrolysis and erythema multiforme) The occurrence of a rash is a definite indication to withdraw medication.

Cardiac / Vascular disorders: Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Hypotension and palpitations have been reported rarely.

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) (see section 4.4)

Respiratory, thoracic and mediastinal disorders: Asthma, dyspnoea.

Other adverse events reported less commonly include:

Renal and urinary disorders: Nephrotoxicity in various forms, including renal papillary necrosis. As with other prostaglandin inhibitors allergic glomerulonephritis has occurred occasionally. There have also been reports of acute interstitial nephritis, dysuria, with haematuria, proteinuria, renal failure including renal papillary necrosis and occasionally nephroitic syndrome.

Non-oliguric renal failure has been reported on a few occasions in elderly patients with dehydration usually from diarrhoea. Toxicity has been seen in patients with pre-renal condition leading to a reduction in renal blood flow or blood volume. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, and liver dysfunction those taking diuretics and elderly. The drug should not be administered to patients with significantly impaired renal function. It has been suggested that the recovery is more rapid and complete with other forms of analgesic induced renal

impairment, with discontinuation of NSAID therapy being typically followed by recovery to the pre-treatment state.

Hepato-bilary disorders: Borderline elevations of one or more liver function tests may occur in some patients receiving mefenamic acid therapy. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should have their therapy discontinued. Patients on prolonged therapy should be kept under surveillance with particular attention to liver dysfunction. Mild hepatotoxicity, hepatorenal syndrome, hepatitis and cholestatic jaundice have been reported with NSAID therapy.

Nervous system disorders: headaches, paraesthesia, reports of aseptic meningitis (especially in patients with auto- immune disorders, such as systemic lupus erythematosus mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4), dizziness, malaise, fatigue and drowsiness, convulsions, insomnia.

Psychiatric disorders: Confusion, depression, hallucinations, nervousness

Eye disorders: Eye irritation, optic neuritis, reversible loss of colour vision, visual disturbances and blurred vision.

Ear and labyrinth disorders: Ear pain, tinnitus, vertigo.

General disorders and administration site conditions: Fatigue, malaise, multi-organ failure, pyrexia.

Blood and lymphatic system disorders: Thrombocytopenia purpura, neutropenia, hypoplasia bone marrow, haematocrit decreased, anaemia, aplastic anaemia has been reported. In some cases reversible haemolytic anaemia has occurred.
Temporary lowering of the white blood cell count (leukopenia) with a risk of infection, sepsis, and disseminated intravascular coagulation, which may have been due to mefenamic acid has been reported. Rarely eosinophilia, agranulocytosis and pancytopenia have been reported. Blood studies should therefore be carried out during long term administration and the appearance of any dyscrasisas is an indication to discontinue therapy.

Skin and subcutaneous tissue disorders: Angioedema, laryngeal oedema, erythema multiforme, face oedema, bullous reactions including Lyell's syndrome ((toxic epidermal necrolysis, (very rare)) and Stevens-Johnson syndrome, perspiration, rash, photosensitivity reaction, purpura, fixed drug eruption (see Immune system disorders for other skin reactions), pruritus and urticaria.

Metabolism and nutritional disorders: Glucose intolerance in diabetic patients has been reported rarely. Hyponatraemia

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

Reporting suspected adverse reactions after authorisation 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9. Overdose

a) Symptoms

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, epigastric pain, gastrointestinal bleeding disorientation excitation, coma, drowsiness, dizziness, tinnitus, fainting, occasionally convulsion. In cases of significant poisoning acute renal failure and liver damage are possible.

Mefenamic acid has a tendency to induce tonic-clonic (grand mal) convulsion in overdose.

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 adults, 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 lest 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

M01 A G01 Anti-inflammatory and anti- rheumatic products, non-steroids, Fenamates.
Mefenamic acid belongs to the family of drugs called fenamates, which are aspirin-like drugs that are derivatives of N-phenylanthranilic acid. In tests of anti-nflammatory activity, mefenamic acid is about half as potent as phenylbutazone. Mefenamic acid has antipyretic and analgesic properties and displays a central as well as a peripheral action. Mefenamic acid appears to owe these properties to its capacity to inhibit cyclo-oxygenase.

5.2. Pharmacokinetic Properties

Peak concentrations in plasma are reached in 2 to 4 hours and the half-life of the drug is also 2 to 4 hours.
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.
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.

In man, approximately 50% of a dose of mefenamic acid is excreted in the urine. Of this, approximately half is the conjugated 3-hydroxymethyl metabolite, a little less than half is the 3-carboxyl metabolite and its conjugates, and the remaining few percent is mostly conjugated mefenamic acid.

Twenty percent of the drug is recovered in the faeces, mainly as the unconjugated 3-carboxyl metabolite.

5.3 Preclinical safety data

Not available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Gelatin,
Sodium starch glycollate,
Sodium laurilsulfate.

Capsule shell excipients:
Patent blue V (E131),
Erythrosine (E127),
Titanium dioxide (E171),
Yellow iron oxide (E172),
Gelatin.

6.2 Incompatibilities

None known.

6.3. Shelf Life

5 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Plastic securitainers with polypropylene lids with double security closure containing Mefenamic Acid capsules (material of the container complies with EEC directives for plastic in contact with food stuff and drug), dispended in the pack sizes of 50, 84, 100, 250, 500 and 1000 capsules.

Blisters packs consisting of 0.25mm PVC and 0.020mm aluminium foil in pack sizes of 14, 28, 56, 84 and 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Pharmvit Limited
177 Bilton Road
Perivale
Greenford
Middlesex
UB6 7HQ

8 MARKETING AUTHORISATION NUMBER(S)

PL 4556/0045

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/08/2025

10 DATE OF REVISION OF THE TEXT

29/08/2025