

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mefenamic Acid 250 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Mefenamic Acid 250 mg

Excipient(s) with known effect

Lactose Monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard

Hard gelatin capsule with a blue cap and a buff body, printed with “MEF 250” both on body and cap.

4. CLINICAL PARTICULARS

4.1. Therapeutic 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

For oral administration

The capsules should be swallowed with a drink of water. To be taken preferably with or after food.

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

Adults: 2 capsules (500mg) three times daily

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:

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 for GI bleeding during NSAID therapy.

Children (under 12 years): Not recommended

4.3 Contraindications

- Hypersensitivity to mefenamic acid or to any of the excipients.
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g asthma, bronchospasm, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.
- Severe hepatic, renal and cardiac failure (See section 4.4)
- During the last trimester of pregnancy (See section 4.6)
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Mefenamic acid should not be administered to patients with inflammatory bowel disease (e.g ulcerative colitis, Crohn's disease)
- Treatment of pain after coronary artery bypass graft (CABG) surgery.

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest 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 specific 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).

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 dependent 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 (see also section 4.3).

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 (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available.

Combination therapy with protective agents (e.g. misoprostal 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, 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, or anticoagulants such as warfarin, selective serotonin reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

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).

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 (see section 4.8).

Dermatological:

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens Johnson syndrome, and toxic epidermal necrolysis, have been reported 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.

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.

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.

Gynaecological:

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

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.

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4). Concurrent administration of mefenamic acid with oral anticoagulant 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: Decreased elimination of lithium. 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 Capsules:

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 (see section 4.4).

Antidepressants: selective serotonin reuptake inhibitors (SSRIs):
Increased risk of gastrointestinal bleeding (see section 4.4).

Anti-hypertensives and diuretics: Reduced anti-hypertensive effect and reduced diuretic effect. Diuretics can increase the risk of 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 bleeding or ulceration (see section 4.4).

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 glycoside levels.

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

Corticosteroids: Increased risk of gastro-intestinal bleeding or ulceration (see section 4.4).

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 used for 8 – 12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

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

Quinolone 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.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine: Possible 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 and ibuprofen.

4.6. 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 (see section 4.3 – Contraindications). 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.

Lactation:

In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. Therefore, mefenamic acid should not be taken when breastfeeding.

See section 4.4 - Special warning and precautions for use, regarding female fertility.

4.7. Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible undesirable effects 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 lymphatic system disorders:

Thrombocytopenia, neutropenia, agranulocytosis, anaemia, haemolytic anaemia and aplastic anaemia have been reported.

In some cases reversible haemolytic anaemia has occurred. Temporary lowering of the white blood cell count (leukopenia) with a risk of infection 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 dyscrasia is an indication to discontinue therapy. Hypoplasia bone marrow, haematocrit decreased, thrombocytopenic purpura, sepsis and disseminated intravascular coagulation has also 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 and bullous dermatoses (including epidermal necrolysis and erythema multiforme). The occurrence of a rash is a definite indication to withdraw medication.

Nervous system: Optic neuritis, headaches, paraesthesia, 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 (see section 4.4), dizziness, and drowsiness, convulsions, insomnia, blurred vision.

Psychiatric Disorders: depression, confusion, hallucinations, nervousness

Eye disorders: Visual disturbances, eye irritation, reversible loss of colour vision,

Ear and labyrinth disorders: Tinnitus, vertigo, ear pain

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).

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 (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) 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.

Also reported anorexia, colitis, enterocolitis, gastric ulceration with or without haemorrhage, pancreatitis, and steatorrhea.

Hepato-biliary 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. Hepatitis and cholestatic jaundice have been reported with NSAID therapy.

Also reported mild hepatotoxicity and hepatorenal syndrome.

Skin and subcutaneous tissue disorders:

Bullous reactions including Stevens Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome, very rare). Photosensitivity, purpura, angioedema, laryngeal oedema, erythema multiforme, face oedema, perspiration, pruritus, rash and urticaria

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 with haematuria and proteinuria and occasionally nephrotic syndrome. Dysuria.

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, liver dysfunction,

those taking diuretics and the 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.

General disorders and administration site conditions

Malaise, fatigue. Multi-organ failure, pyrexia

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.

Respiratory, thoracic and mediastinal disorders

Asthma, dyspnoea

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 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

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

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 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

M01A G01 Anti-inflammatory and antirheumatic products, non-steroids. Fenamates

Mefenamic acid is a nonsteroidal anti-inflammatory drug (NSAID) with antiinflammatory, 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 brewers 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 (cyclo oxygenase). 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

Absorption and distribution

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

Metabolism

Mefenamic acid is extensively metabolized 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

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 per cent 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

No data of relevance which is additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose Monohydrate
Gelatin
Sodium Starch Glycollate
Sodium Laurilsulfate

Capsule Shell:

Patent Blue V (E131)
Erythrosine (E127)
Titanium Dioxide (E171)
Yellow Iron Oxide (E172)
Gelatin

Printing Ink (Opacode S-1-8100HV Black Ink):

Shellac
Black Iron Oxide (E172)
Soya Lecithin
Dimeticone

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

4 years.

6.4. Special precautions for storage

Do not store above 30°C.

6.5. Nature and contents of container

1. Polypropylene tubes with low density polyethylene caps. High density polyethylene film may be used as packing material.

2. Snap-Safe Vials: Child resistant containers consisting of polypropylene tubes with high density polyethylene caps.

Pack sizes: 50, 84, 100, 250, 500 and 1000 capsules.

Not all pack sizes may be marketed.

6.6. Instructions for use and handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Strides Pharma UK Ltd
Unit 4, Metro Centre
Tolpits Lane
Watford
Hertfordshire
WD18 9SS
Trading as: Co-pharma

8. MARKETING AUTHORISATION NUMBER

PL 13606/0119

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16th May 2005

10 DATE OF REVISION OF THE TEXT

18/10/2017