SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mefenamic Acid 500 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg mefenamic acid.

Excipient with known effect:
Sunset Yellow (E110)

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets
Pale yellow, ovoid, film coated tablets, engraved "3P2" on one side, plain reverse.

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. Mefenamic acid is an anti-inflammatory analgesic for the symptomatic relief of rheumatoid arthritis (including Still's disease), osteoarthritis and for the relief of mild to moderate pain including headaches of most aetiology, traumatic and dental pain, muscular pain, post-operative and post-partum pain.
2. primary dysmenorrhoea.
3. menorrhagia due to dysfunctional causes and the presence of an IUD when other pelvic pathology has been ruled out.

4.2 Posology and method of administration

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

For oral administration. Should be taken preferably with or after food.

Adults

1 tablet (500 mg) three times daily.

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

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

Children

It is recommended that children under 12 years of age should be given mefenamic acid Suspension (50mg/5ml).

The Elderly (over 65 years)

As for adults.

Whilst no pharmacokinetic or clinical studies specific to the elderly have been undertaken with mefenamic acid, it has been used at normal dosage in trials which included many elderly patients.

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

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

Do not exceed the stated dose.

4.3 Contraindications

Hypersensitivity to mefenamic acid or to any of the excipients.

Inflammatory bowel disease

History of upper gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Active or history or recurrent peptic ulcer/ haemorrhage (two or more distinct episodes of proven ulceration or bleeding)

Severe heart failure hepatic failure and renal failure (See section 4.4).

Because the potential exists for cross-sensitivity to aspirin, ibuprofen, or other non-steroidal anti-inflammatory 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 (see section 4.6).

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

4.4 Special Warnings and special 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).

The use of mefenamic acid with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (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 administrated 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 (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. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low 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 ulceration or bleeding, such as corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (See section 4.5 – Interactions).

When GI bleeding or ulceration occurs in patients receiving Mefanamic 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).

SLE and mixed connective tissue diseases:
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 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 the 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 risk, mucosal lesions, or any other sign of hypersensitivity.

Female fertility:
The use of mefanamic 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 mefanamic acid should be considered.

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

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.

Epilepsy:
In patients suffering from epilepsy caution should be exercised during treatment.

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).

Excipient(s)

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

Sunset yellow may cause allergic-type reactions.

4.5 Interaction with other medicaments 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 mefenamic acid 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 (see section 4.4).

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

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 (see section 4.4).

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 gastrointestinal ulceration or bleeding (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 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 hematological 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 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.

From the 20th week of pregnancy onward, Mefenamic Acid use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, Mefenamic Acid should not be given unless clearly necessary. If Mefenamic Acid is used by a woman attempting to

conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Mefenamic Acid for several days from gestational week 20 onward. Mefenamic Acid should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

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.

Consequently, Mefenamic Acid is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Breast-feeding
Trace amounts of mefenamic acid may be present in breast milk and transmitted to the nursing infant. Therefore, mefenamic acid should not be taken by nursing mothers.

See section 4.4 – Special warnings 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 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 (leucopenia) 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.

Pyschiatric 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 (see section 4.4).

Blurred vision, convulsions, insomnia.

Eye disorders
Eye irritation, reversible loss of colour vision, visual disturbances.

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) (see section 4.4).

Palpitations.

Hypotension.

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 (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, 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, jaundice, 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.

Renal and urinary disorders
Allergic glomerulonephritis, acute interstitial nephritis, dysuria, haematuria, nephrotic syndrome, nonoliguric renal failure (particularly in dehydration), proteinuria, renal failure including renal papillary necrosis, nephrotoxicity in various forms,.

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
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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

a) Symptoms

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

b) Therapeutic measures

Patients should be treated symptomatically as required.

Within one hour of ingestion of a particularly 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

ATC Code: MO1A GO1 Fenamates

ANIMAL MODELS

Mefanamic acid is a non-steroidal anti-inflammatory drug (NSAID) and has 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 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 (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.

Pharmacokinetic properties

Absorption and Distribution

Mefenamic acid is absorbed from the gastrointestinal tract. Peak levels of 10 mg/l occur two hours after 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 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.

5.3 Preclinical safety data

Preclinical information has not been included because the safety profile of mefenamic acid has been established after many years of clinical use. Preclinical safety data does not add anything of further significance to the prescriber. Please refer to section 4.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Calcium Phosphate
Croscarmellose sodium
Povidone
Sodium laurilsulfate
Stearic Acid
Polyvinyl alcohol-partially hydrolysed
Titanium dioxide (E171)
Macrogol/PEG
Talc
Quinolene yellow (E104)
Iron oxide yellow (E172)
Sunset yellow (E110)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 25°C. Store in the original package.

6.5 Nature and contents of container

HDPE containers with LDPE lids in packs of 60, 100, 250 or 500 tablets.

Ward packs (amber glass bottles with plastic screw caps or HDPE containers with LDPE lids) in a pack of 50 tablets.

PVdC coated PVC film with hard tempered aluminium foil blister strips in packs of 7, 10, 14, 21, 28, 30, 56, 60, 84, 90, 100, 110, 112, 120, 150, 160, 168 or 500 tablets.

HDPE containers with child resistant closures in a pack of 84 tablets.

Not all pack sizes may be marketed.

6.6 Instructions for use/handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Teva UK Limited
Ridings Point,
Whistler Drive,
Castleford, WF10 5HX,
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00289/0235

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

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10. DATE OF (PARTIAL) REVISION OF THE TEXT

10/03/2023

POM