SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Mefenamic Acid DAWA 250 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250mg of Mefenamic acid.

Excipients with known effect

Each tablet contains 25.0 mg lactose monohydrate.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated Tablets

Yellow coloured, oval shaped, 15.10mm x 6.30mm, film coated tablets plain on both sides.

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

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

Do not exceed the stated dose.

Posology

Adults

2 tablets (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 treatment of dysmenorrhoea it should 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 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.

Paediatric population

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

Method of administration

For oral administration.

Mefenamic acid should be taken preferably with or after food.

4.3 Contraindications

- Hypersensitivity to the active substance or any of the excipients listed in section 6.1.

- 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, 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 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 specific 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.

<u>Elderly:</u>

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 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 and/or 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. 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 (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, 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.

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).

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 the use of NSAIDs (see section 4.8). 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 the lack of response should alert the physician to investigate other causes.

Epilepsy:

Caution should be exercised when treating patients suffering from epilepsy.

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).

Alcohol

Concomitant consumption of alcohol with mefenamic acid may increase the risk of gastrointestinal bleeding, ulceration and perforation.

Excipients

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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.

Anticoagulants: NSAIDs may enhance the effects of anticoagulants, 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: 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).

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

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

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

Corticosteroids: Concomitant use may increase the risk of gastrointestinal ulceration or bleeding (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 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 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 (see section 4.3). 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.

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.

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 (with 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.

Breastfeeding

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.

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 (see section 4.4).

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 nutrition 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 (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.

Hepatobiliary 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.

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 and administration site conditions

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 website: 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.

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.

Management

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

Pharmacotherapeutic group: Anti-inflammatory and anti-rheumatic products, non-steroids, fenamates. ATC code: M01AG01

Mechanism of action

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 carrageenan 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.

5.2 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.

Biotransformation

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose Monohydrate

Pregelatinized Starch

Croscarmellose Sodium

Povidone

Microcrystalline cellulose

Colloidal Silicon Dioxide

Magnesium Stearate

Tablet coat

Hypromellose (E464), lactose monohydrate, titanium dioxide (E171), polyethylene glycol (E1521), iron oxide yellow (E172), talc (E553b), iron oxide red (E172).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

48 months

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Tablets are packed in a blister made of PVC/PVDC and aluminium foil.

Pack size: 28, 84 and 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

DAWA Limited

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Harrow Middlesex

HA1 1XD

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8 MARKETING AUTHORISATION NUMBER(S)

PL 30684/0341

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

30/09/2024