Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

MEFAC 500 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains mefenamic acid 500 mg.
Excipients(s) with known effect:
Also contains Sunset Yellow (E110), approximately 0.0625 per tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablets.

Yellow oval film coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Mefac is indicated in adults only;

- as an anti-inflammatory analgesic for symptomatic relief of mild to moderate pain associated with rheumatic muscular or arthritic disorders (including rheumatoid arthritis and osteoarthritis), trauma, headache, dental pain, post-operative or post-partum states;

- in the management of dysfunctional menorrhagia;

- primary dysmenorrhoea;

- premenstrual syndrome.

4.2 Posology and method of administration

Posology

Adults Only: The usual total daily dose is 1500mg in divided doses.

Elderly patients: NSAIDs should be used with particular caution in elderly patients who are more prone to adverse events, especially with long-term use. Therefore, the risks versus the benefits of chronic therapy in the elderly should be carefully considered. The lowest dose compatible with adequate safe clinical control should be employed. (See also Section 4.4)

Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

Paediatric population: Not recommended for children under 12 years of age.

Do not exceed the stated dose.

Method of Administration

Mefac should be taken preferably with or after food.

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

4.3 Contraindications

- Use in patients with intestinal ulceration or inflammation and in patients with inflammatory bowel disease.
- Use in patients with a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Use in patients with an active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Use in patients with renal or hepatic impairment.
- Use in patients with severe heart failure
- Use in pregnancy or lactation (see section 4.6)
- Use in patients shown to be hypersensitive (e.g. asthma, bronchospasm, rhinitis, angioedema, urticaria) to the active substance, any of the excipients listed in section 6.1, aspirin, ibuprofen or other non-steroidal anti-inflammatory drugs.
- Use with concomitant NSAIDs including cyclooxygenase 2 specific inhibitors (see section 4.5)
- 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 discontinue therapy immediately.

Precaution should be taken in patients suffering from dehydration and renal disease, particularly the elderly.

Prolonged use of NSAIDs in the elderly is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

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.

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 higher 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 lesion, or any other sign of hypersensitivity.

SLE and mixed connective tissue disorder: 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).

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 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).

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

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).

Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation which can be fatal, has been reported for 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 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 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 oral 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.

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

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

In dysmenorrhoea and menorrhagia, lack of response to mefenamic acid 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 substrate, mefenamic acid should be administered with caution as they may have abnormally high plasma levels due to reduced metabolic clearance (see section 5.2).

The tablet coating contains the colouring agent sunset yellow which may cause allergic reactions.

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

4.5 Interaction with other medicinal products and other forms of interactions

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

Anti-coagulants: NSAIDs may enhance the anticoagulant effect, 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 an 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 necessary been associated with Mefac:

Other analgesics: concomitant use of two or more NSAIDs (including aspirin) should be avoided (see section 4.3)

Antidepressants: selective serotonin reuptake inhibitors (SSRIs): increased risk of gastro-intestinal bleeding (see section 4.4)

Anti-hypertensives: reduced anti-hypertensive effect

Diuretics: 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 (see section 4.4)

Cardiac glycosides: NSAIDs may exacerbate cardiac failure and increases in plasma cardiac glycoside levels may occur when renal function is affected.

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

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

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

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

Methotrexate: elimination of methotrexate can be reduced resulting in increased plasma levels.

Probenecid: reduction in metabolism and elimination of NSAID 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 increased risk of developing convulsion.

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

Zidovudine: Increase risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemaophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy has not been established and because of the effects of drugs in this class on the foetal cardiovascular system, the use of mefenamic acid in pregnant women is not recommended (see section 4.3). 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 4.3)

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

a) General Description

The most frequently reported side effects associated with mefenamic acid involve the gastrointestinal tract. Diarrhoea appears to be the most common side effect and is usually dose-related. It generally subsides on dosage reduction, and rapidly disappears on termination of therapy. Some patients may not be able to continue therapy.

b) Table of adverse reactions

Frequency of reactions: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders
Frequency not known: autoimmune haemolytic anaemia (see section c, Information characterising individual serious and/or frequently occurring adverse reactions), 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

Rare: agranulocytosis, aplastic anaemia, eosinophilia, neutropenia, pancytopenia

Immune system disorders
Frequency not known: anaphylaxis

Metabolism and nutritional disorders
Frequency not known: glucose intolerance in diabetic patients, hyponatraemia

Psychiatric disorders
Frequency not known: nervousness

Nervousn system disorders
Frequency not known: aseptic meningitis, blurred vision, convulsions, dizziness, drowsiness, headache and insomnia

Eye disorders
Frequency not known: eye irritation, reversible loss of colour vision

Ear and labyrinth disorders
Frequency not known: ear pain

Cardiac disorders
Frequency not known: palpitations

Vascular disorders
Frequency not known: hypotension

Respiratory, thoracic and mediastinal disorders
Frequency not known: asthma, dyspnoea

Gastrointestinal disorders
Frequency not known: abdominal pain, diarrhoea (see section c, Information characterising individual serious and/or frequency occurring adverse reactions) and nausea with or without vomiting.

Less frequent: anorexia, colitis, constipation, dyspepsia, enterocolitis, flatulence, gastric ulceration with or without haemorrhage, pancreatitis, steatorrhea

Hepato-biliary disorders
Frequency not known: borderline elevations of one or more liver function tests, cholestatic jaundice
Less frequent: mild hepatotoxicity, hepatitis, hepatorenal syndrome

Skin and subcutaneous tissue disorders
Frequency not known: angioedema, laryngeal oedema, erythema multiforme, face oedema, Lyell's syndrome (toxic epidermal necrolysis), perspiration, rash, Stevens-Johnson syndrome, photosensitivity reaction and urticaria.

Renal and urinary disorders
Frequency not known: 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
Very rare: multi-organ failure, pyrexia

c) Information characterising individual serious and/or frequently occurring adverse reactions

Reversible haemolytic anaemia: Reports are associated with ≥ 12 months of mefenamic acid therapy and the anaemia is reversible with discontinuation of treatment.

Diarrhoea: although this may occur soon after starting treatment, it may also occur after several months of continuous use. If diarrhoea persists then inflammatory bowel disease should be excluded; if present mefenamic acid must be stopped.

Note: 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.

d) Adverse reactions which may not have been observed but which are generally accepted as being attributable to other NSAIDs

Hypersensitivity: 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, angiodema, and more rarely exfoliative or bullous dermatoses, including epidermal necrolysis, toxic epidermal necrolysis (Lyell's syndrome), erythema multiforme and Stevens-Johnson syndrome.

Neurological and special senses: Visual disturbances, optic neuritis, 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), depression, confusion, hallucinations, tinnitus, vertigo, malaise, fatigue and drowsiness.

Cardiovascular: 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).

Gastrointestinal: 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, melaenia, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease have been reported following administration. Less frequently, gastritis has been observed.

Additional information on special populations

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.

Renal toxicity has been seen in patients with pre-renal conditions 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.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: http://www.hpra.ie/; e-mail: medsafety@hpra.ie.

4.9 Overdose

Gastric lavage in the conscious patients and intense supportive therapy where necessary. Vital functions should be monitored and supported. Activated charcoal has been shown to be a powerful absorbent for mefenamic acid and its metabolites. Studies in experimental animals and human volunteers have shown that a 5 to 1 ratio of charcoal to mefenamic acid results in considerable suppression of absorption of the drug. Haemodialysis is of little value since mefenamic acid and its metabolites are firmly bound to plasma proteins. Overdose has led to fatalities.

Mefenamic acid has a tendency to induce tonic-clonic (grand mal) convulsions in overdose. Acute renal failure and coma have been reported with mefenamic acid overdose. It is important that the recommended dose is not exceeded and the regime adhered to since some reports have been involved daily dosages under 3g.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fenamates, ATC code: M01AG01
ANIMAL MODELS

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 10mg/l occur two hours after the administration of a 1g oral dose to adults.

Metabolism: Mefenamic acid is predominantly metabolised by cytochrome P450 enzyme CYP2C9 in the liver, first to a 3 hydroxymethyl derivative (metabolite I) and then a 3 carboxyl derivative (metabolite II). Both metabolites undergo secondary conjugation to form glucuronides.

Therefore in patients who are known or suspected to be poor CYP2C9 metabolisers based on previous history/experience with other CYP2C9 substrates, mefenamic acid should be administered with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Elimination: Fifty two percent of a dose is recovered from the urine, 6% as mefenamic acid, 25% as metabolite I and 21% as metabolite II. Assay of stools over a 3 day period accounted for 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
Microcrystalline cellulose
Povidone
Sodium starch glycollate Type A
Magnesium stearate

Tablet coating
Opadry OY 8494 Yellow containing:
Hypromellose (E464)
Titanium dioxide (E171)
Quinoline yellow (E104)
Sunset yellow (E110)
Indigo Carmine (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

MEFAC Tablets 500 mg are packed in white polypropylene tablet containers with matt white polyethylene circular caps. The caps have tear-strips fully attached all around and a pull-off lip above the tear-strip. MEFAC tablets are available in sales packs of 100 tablets and sample packs of 6 tablets are also available.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowa Pharmaceuticals Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0074/015/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th April 1988

Date of last renewal: 28th April 2008

10 DATE OF REVISION OF THE TEXT

April 2019