

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0405/014/001

Case No: 2042222

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Generics (UK) Limited

12 Station Close, Potters Bar, Hertfordshire EN6 1TL, United Kingdom

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Mefenamic Acid 250mg Capsules BP

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **17/06/2008**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mefenamic Acid 250mg Capsules BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg of Mefenamic Acid

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule, hard

Size 1, hard gelatin capsule with an opaque yellow body and an opaque blue cap, marked with 'MA 250' and 'G', containing a white, granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. As an anti-inflammatory analgesic for symptomatic relief of mild to moderate pain associated with rheumatic, muscular or arthritic disorders (including rheumatoid arthritis, Stills Disease and osteoarthritis), trauma, headaches, dental pain, post-operative or post-partum states.
2. For control of pyrexia in children.
3. In the management of dysfunctional menorrhagia.
4. Primary dysmenorrhoea.
5. Premenstrual Syndrome.

4.2 Posology and method of administration

For oral administration.

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

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

Elderly: 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 precautions and warnings.

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

Children:

Not recommended for children under 12 years of age.

Do not exceed the stated dose.

Mefenamic Acid should be taken preferably with or after food.

4.3 Contraindications

1. Use in patients with intestinal ulceration or inflammation and in patients with inflammatory bowel disease.
2. Use in patients with a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
3. Use in patients with active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
4. Use in patients with severe heart failure.
5. Use in pregnancy or lactation (See Section 4.6 Pregnancy and Lactation)
6. Use in patients with renal or hepatic impairment.
7. Patients with a history of hypersensitivity reactions (e.g. asthma, bronchospasm, rhinitis, angioedema, urticaria) in response to Mefenamic Acid, any of the other ingredients of Mefenamic Acid capsules, aspirin, ibuprofen or other non-steroidal anti-inflammatory drugs.
8. Use with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors (See Section 4.5 Interactions).

4.4 Special warnings and precautions for use

Patients treated with NSAIDs long-term should undergo regular medical supervision to monitor for adverse events.

In patients with renal, cardiac or hepatic impairment, caution is required since to use of NSAIDs may result in deterioration of renal function. Assessment of renal function should occur prior to the initiation of therapy and regularly thereafter.

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

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

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 with all NSAIDs at anytime 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 4.5).

Patients with a history of GI toxicity, particularly when elderly, should report and 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 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 Capsules, 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.

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.

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 should alert the physician to investigate other causes.

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 4.8). Patients appear to be at higher 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 Capsules should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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 - Undesirable effects).

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.

Patients on prolonged therapy should be kept under regular surveillance with particular attention to liver dysfunction, rash, blood dyscrasis or development of diarrhoea.

Appearance of any of these should be regarded as an indication to discontinue therapy immediately.

Caution should be exercised when treating patients suffering from epilepsy.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent administration with protein bound drugs such as anticoagulants may require adjustment in their 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 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.

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

Anti-hypertensives: reduced anti-hypertensive effect.

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

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

Lithium: decreased elimination of lithium.

Methotrexate: decreased elimination of methotrexate.

Cyclosporin: increased risk of nephrotoxicity with NSAIDs.

Other NSAIDs: avoid concomitant use of two or more NSAIDs (including aspirin).

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

Aminoglycosides: reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.

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

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

Diuretics, ACE inhibitors and Angiotensin II Antagonists: NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking Mefenamic Acid concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

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

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

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

Quinolone antibiotics: animal data indicated that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolone may have an increased risk of developing convulsions.

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

4.6 Pregnancy and lactation

Safety in pregnancy and lactation 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 Contraindications).

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 Contraindications).

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $\leq 1/100$); rare ($\geq 1/10,000$ to $\leq 1/1000$); very rare ($\leq 1/10,000$), not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders

Frequency not known: autoimmune haemolytic anaemia (see section c), 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

Nervous 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) 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, angioedema, 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, melaena, 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.

4.9 Overdose

Gastric lavage in the conscious patient and intensive 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 humans 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 involved daily dosage under 3g.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinflammatory and antirheumatic products, non steroids (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 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

Mefenamic acid is absorbed from the gastro intestinal tract. Peak levels of 10 mg/l occur two hours after the administration of a 1g oral dose to adults.

Metabolism

Mefenamic acid is extensively metabolised, first to a 3 hydroxymethyl derivative (metabolite I) and then a 3 carboxyl derivative (metabolite II). Both metabolites undergo secondary conjugation to form glucuronides.

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 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

There are no pre-clinical data of relevance to the prescriber which are additional to the warnings already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone
Microcrystalline Cellulose
Pregelatinised Maize Starch
Sodium Starch Glycolate (Type A)
Magnesium Stearate
Purified Talc
Croscarmellose Sodium
Polysorbate 80

Capsule Shell
Gelatin
Patent Blue V (E131)
Titanium Dioxide (E171)
Yellow Iron Oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

Polypropylene containers: 3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Polypropylene containers with polyethylene caps in packs of 30, 100, 250 and 500 capsules.

Not all pack sizes may be marketed

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

Generics (UK) Limited
Station Close
Potters Bar
Hertfordshire, EN6 1TL
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 405/14/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st May 1987

Date of last renewal: 21st May 2007

10 DATE OF REVISION OF THE TEXT

June 2008