IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA1046/002/001
Case No: 2034428

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

Winthrop Pharmaceuticals UK Limited

One Onslow Street, **Guildford**, **Surrey**, **GU1 4YS**, **United Kingdom**

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

MEFENAMIC ACID 250mg Capsules

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 **09/07/2007** until **16/12/2007**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mefenamic Acid 250 mg Capsule

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Mefenamic Acid 250 mg

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.
Blue/yellow gelatin capsule.

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 arthritis disorders (including rheumatoid arthritis, Still's Disease and osteo-arthritis) trauma, headache, dental pain, post-operative or post-partum states.
2. Primary dysmenorrhoea.
3. In the management of dysfunctional menorrhagia.
4. Premenstrual syndrome.

4.2 Posology and method of administration

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

Adults
The usual dose is 1500 mg in divided doses.

In menorrhagia, mefenamic acid should be administered on the first day of excessive bleeding and continued according to the judgment of the physician.

In dysmenorrhoea, mefenamic acid should be administered at the onset of menstrual pain and continued according to the judgment of the physician.

Elderly (over 65 years)
As for adults.

NSAIDs should be used with particular caution in elderly patients who are more prone to adverse events. 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.

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

Children
The tablets/ capsules are not recommended for children under 12 years.

4.3 Contraindications

1. History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes or proven ulceration or bleeding).

2. Use in pregnancy or lactation.

3. Use in patients with renal or hepatic impairment.

4. Use in patients shown to be hypersensitive to mefenamic acid, aspirin or other NSAIDs.

5. Severe heart failure.

4.4 Special warnings and precautions for use

The use of Mefenamic Acid 250mg Capsules with concomitant NSAIDs including cyclooxygenase-2-selective inhibitors should be avoided.

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

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

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.

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 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 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 250mg Capsules, 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 their condition may be exacerbated (see section 4.8 – undesirable effects).

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 the 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 250mg Capsules should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Cardiovascular and cerebrovascular
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, (particulary 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 events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

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

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

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

Caution should be exercised when treating patients suffering from epilepsy.

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 should be regarded as an indication to discontinue therapy immediately.

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Anticoagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4). Concurrent administration with protein bound drugs such as anticoagulants may require adjustment in their dosage. In case of anticoagulants the dose of the anticoagulant may need to be reduced due to enhanced anticoagulant effect.

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 effects.

Diuretics: Reduced diuretics effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

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

Lithium: Decreased elimination of lithium.

Methotrexate: Decreased elimination of methotrexate.

Ciclosporin: Increased risk of nephrotoxicity with NSAIDs.

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

Other NSAIDs: Avoid concomitant use of two or more NSAIDs.

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

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

Quinolone antibiotics: Animal data indicate 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.

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

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

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

4.6 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 contraindicated.

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.

4.7 Effects on ability to drive and use machines

Drowsiness and dizziness have rarely been reported.

4.8 Undesirable effects

Gastrointestinal disorders:
Nausea vomiting and abdominal pain have been reported. 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.

Serious gastrointestinal toxicity such as bleeding, ulceration and perforation can occur at any time with or without warning symptoms, in patients treated chronically with NSAIDs therapy. In some cases GI bleeding has been associated with a previous history of peptic ulcer, smoking and alcohol use.

Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population.

Skin disorders:
Skin rashes have been observed following the administration of mefenamic acid and occurrence of a rash is a definite indication to withdraw medication. Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (very rare).

Renal and urinary disorders:
As with other prostaglandin inhibitors allergic glomerulonephritis has occurred occasionally. There have also been reports of acute interstitial nephritis with haematuria and proteinuria and occasionally nephrotic syndrome. Non-oliguric renal failure has been reported on a few occasions in elderly patients with dehydration usually from diarrhoea.

Toxicity has been seen in patients with pre-renal 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. The drug should not be administered to patients with significantly impaired renal function. It has been suggested that the recovery is more rapid and complete than with other forms of analgesic induced renal impairment, with discontinuation of NSAID therapy being typically followed by recovery to the pre-treatment state.

Cardiovascular disorders:
There have been rare reports of hypotension and palpitations. Oedema, hypertension and cardiac failure have been repor 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 a small increased risk of arterial thrombotic events (for example myocardial infarctio or stroke) (see section 4.4).

Nervous system disorders:
Headache, drowsiness and dizziness have been reported rarely.

Blood and lymphatic system disorders:
Thrombocytopenia has been reported with mefenamic acid. In some cases reversible haemolytic anaemia has occurred. Temporary lowering of the white blood cell count which may have been due to mefenamic acid has been reported. Rarely eosinophilia, agranulocytosis and pancytopenia and aplastic anaemia have been reported. Blood studies should therefore be carried out during long term administration and the appearance of any dyscrasia is an indication to discontinue therapy.

Respiratory disorders:
Bronchospasm and/or urticaria may be precipitated in patients suffering from, or with a previous history of bronchial asthma or allergic disease.

Hepato-biliary disorders:

Borderline elevations of one or more liver function tests may occur in some patients receiving mefenamic acid therapy. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should have their therapy discontinued. Patients on prolonged therapy should be kept under surveillance with particular attention to liver dysfunction. Cholestatic jaundice and pancreatitis have also been reported.

General disorders:
Anaphylaxis, abnormal vision and glucose intolerance in diabetic patients have rarely been reported.

4.9 Overdose

Gastric lavage in the conscious patient and intensive supportive therapy where necessary. Vital function 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 (grandmal) convulsion 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 dosages under 3g.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mefenamic acid is a non-steroidal anti-inflammatory agent with analgesic properties and a demonstrable antipyretic effect. It has also been shown to inhibit prostaglandin activity.

5.2 Pharmacokinetic properties

Mefenamic acid is absorbed from the gastrointestinal tract. Peak concentration in the circulation occur about 2 to 4 hours after ingestion. Mefenamic acid is extensively bound to plasma proteins.

Approximately 50% of a dose may be recovered in the urine within 48 hours, mainly as conjugated metabolites.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Sodium lauryl sulphate
Povidone
Talc
Silicon dioxide
Croscarmellose sodium
Magnesium stearate
Gelatin
Patent blue V (E131)
Titanium dioxide (E171)
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package (blisters).
Keep container tightly closed (bottles).

6.5 Nature and contents of container

i) PVC blister consisting of transparent colourless unplasticised polyvinyl chloride (thickness 250 µm) sealed to aluminium foil (thickness 20 µm). The blisters are then packed in a box containing 100 capsules.

ii) HDPE DUMA Bottles with LDPE cap containing 100 or 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

Winthrop Pharmaceuticals UK Limited
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8 MARKETING AUTHORISATION NUMBER

PA 1046/2/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 December 1992

Date of last renewal: 17 December 2002

10 DATE OF REVISION OF THE TEXT

July 2007