IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0126/081/002
Case No: 2035500

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

Clonmel Healthcare Limited

Waterford Road, **Clonmel**, **Co. Tipperary**, **Ireland**

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

Ponmel 500 mg Film-coated Tablets

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 **29/06/2007** until **30/04/2010**.

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

Ponmel 500 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500mg Mefenamic Acid.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
Yellow ovoid tablets, about 18mm in length, marked "M500" on one face and with the Clonmel logo on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

i. For relief of mild to moderate pain associated with rheumatic muscular or arthritic disorders (including rheumatoid arthritis, Still's disease and osteoarthritis), trauma, headache, dental pain, post-operative or post-partum states.

ii. In the management of the pain of dysmenorrhoea.

4.2 Posology and method of administration

Adults only: The usual total daily dose is 1500 - 2000mg in divided doses.

Method of administration: Oral.

This product is not recommended for use in children under 12 years.

Elderly:

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 Special warnings and precautions for use.

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 Special warnings and precautions for use).

4.3 Contraindications

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

iii. Use in patients with renal or hepatic impairment.
iv. Use in patients with a history of hypersensitivity reactions (e.g. bronchospasm, rhinitis, urticaria) in response to mefenamic acid, aspirin or non-steroidal anti-inflammatory drugs.
v. Severe heart failure

4.4 Special warnings and precautions for use

i. 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.

ii. Care should be taken in patients suffering from dehydration and renal disease, especially the elderly.

iii. Undesirable effects may be reduced by using the minimum effective dose for the shortest possible duration necessary to control symptoms (see section 4.2 posology and method of administration, and GI and cardiovascular risks below). Patients treated with NSAIDs long term should undergo regular medical supervision to monitor for adverse events.

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 associated 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 infraction or stroke). There is insufficient data to exclude such a risk for Ponmel.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with Ponmel 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).

v. 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.

vi. Elderly patients are particularly susceptible to the adverse effects of NSAIDs. Prolonged use of NSAIDs in the elderly is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

vii. 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.

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 Contraindications), 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 Interaction with other medicinal prodocuts and other forms of interaction).

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 and bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5 Interaction with other medicinal products and other forms of interaction).

When GI bleeding or ulceration occurs in patients receiving Ponmel, 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).

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

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

ix. Caution should be exercised in when treating patients suffering from epilepsy.

xi The use of Ponmel 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 Ponmel should be considered.

xii. The use of Ponmel with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

xiii. 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.

xiv. Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, has been reported very rarely in association with the use of NSAIDs (see 4.8 Undesirable effects). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of reaction occurring in the majority of cases within the first month of treatment. Ponmel should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersentitivity.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Corticosteroids: increased risk of gastrointestinal bleeding.

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

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

Mifepristone: NSAIDs should be taken for 8-12 days after mifepristone administration. NSAIDs can reduce the effects of mifepristone.

Quinoline antibiotics: Animal data indicated that NSAIDs can increase the risk of convulsions associated with quinoline antibiotics. Patients taking NSAIDs and quinoline may have an increased risk of developing convulsions.

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4 Special warnings and precautions for use)

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

4.6 Pregnancy and lactation

The safety of mefenamic acid in pregnancy has not been determined. The use of mefenamic acid in pregnancy is not recommended as drugs of this type have an effect on the foetal cardiovascular system. Nursing mothers should not take mefenamic acid as very small amounts may be found in the breast milk and transmitted to the nursing infant.

4.7 Effects on ability to drive and use machines

Drowsiness and dizziness have rarely been reported.

4.8 Undesirable effects

Diarrhoea has been reported occasionally 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 to use this drug in spite of its continued presence. These patients were found to have associated proctocolitis. If diarrhoea does develop the drug should be discontinued immediately and this patient should not receive mefenamic acid again.

Skin rashes have been observed following the administration of mefenamic acid and the occurrence of a rash is a definite indication to discontinue medication. There have been rare reports of Stevens-Johnson syndrome, Lyell’s syndrome (toxic epidermal necrolysis) and erythema multiforme.

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 Special warnings and precautions for use). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, maleana, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see sectin 4.4 Special warnings and precautions for use) have been reported following administration. Less frequently, gastritis has been observed.

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.

As with other prostaglandin inhibitors allergic glomerulonephritis has occurred occasionally. There have been reports of acute interstitial nephritis with haematuria and proteinuria and occasionally nephritic 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 given 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.

Thrombocytopenic purpura 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, aplastic anaemia and pancytopenia have been reported. Therefore, blood studies should be carried out during long term administration and the appearance of any dyscrasia is an indication to discontinue therapy.

Bronchospasm and/or urticaria may occur in patients suffering from, or with a previous history of, bronchial asthma or allergic disease.

Borderline elevations of one or more liver 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. Pancreatitis and cholestatic jaundice have also been reported.

Other adverse reactions: nausea, vomiting, abdominal pain, headache, facial oedema, laryngeal oedema and anaphylaxis. Drowsiness, dizziness, abnormal vision, palpitations, glucose intolerance in diabetic patients and hypotension have rarely been reported.

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.

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 a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4 Speical warnings and precautions for use).

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

Mefenamic acid belongs to the family of drugs called fenamates, which are aspirin-like drugs that are derivatives of N-phenylanthranilic acid. In tests of anti-inflammatory activity, mefenamic acid is about half as potent as phenylbutazone. Mefenamic acid has antipyretic and analgesic properties and displays a central as well as a peripheral action. Mefenamic acid appears to owe these properties to its capacity to inhibit cyclooxygenase.

5.2 Pharmacokinetic properties

Peak concentrations in plasma are reached in 2 to 4 hours and the half-life of the drug is also 2 to 4 hours. In may, approximately 50% of a dose of mefenamic acid is excreted in the urine, of this, approximately half is the conjugated 3-hydroxymethyl metabolite, a little less than half is the 3-carboxyl metabolite and its conjugates, and the remaining few percent is mostly conjugated mefenamic acid. Twenty percent of the drug is recovered in the faeces, mainly as the unconjugated 3-carboxyl metabolite.

5.3 Preclinical safety data

No further information provided.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose
Povidone
Sodium Starch Glycolate
Magnesium Stearate

Film-coat excipients

Hypromellose (E464)
Titanium Dioxide (E171)
Quinoline yellow aluminium lake (E104)
Sunset yellow aluminium lake (E110)
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Keep the container tightly closed.

6.5 Nature and contents of container

Polypropylene tube with low density polyethylene caps.

Pack size: 100, 250, 500 and 1000 tablets.

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

Clonmel Healthcare Limited
Waterford Road
Clonmel
County Tipperary

8 MARKETING AUTHORISATION NUMBER

PA 126/81/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 May 1990

Date of last renewal: 01 May 2005

10 DATE OF REVISION OF THE TEXT

June 2007