

## Summary of Product Characteristics

### 1 NAME OF THE MEDICINAL PRODUCT

Ponalgic Forte 500mg Film-Coated Tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 500 mg of Mefenamic Acid.

Excipients: Also contains Lactose Monohydrate

“For a full list of excipients, see section 6.1”

### 3 PHARMACEUTICAL FORM

Film coated tablet.

Caplet shaped yellow film coated tablets embossed with Antigen logo 'a' and 'MA 500' on one side.

### 4 CLINICAL PARTICULARS

#### 4.1 Therapeutic Indications

- 1) For relief of mild to moderate pain associated with rheumatic muscular or arthritic disorders (including rheumatoid arthritis) trauma, headache, dental pain, and post-operative or post-partum states.
- 2) In the management of dysfunctional menorrhagia.
- 3) Primary dysmenorrhoea.

#### 4.2 Posology and method of administration

Route of administration: Oral.

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

Ponalgic capsules should be taken preferably with or after food.

Older people: NSAID's 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.

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

#### 4.3 Contraindications

1. Use in patients with gastric and/or intestinal ulceration or inflammation.
2. 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).
3. Use in pregnancy or lactation (See section 4.6).
4. Use in patients with renal or hepatic impairment.
5. Hypersensitivity to mefenamic acid or to any of the excipients listed in section 6.1.
6. Hypersensitivity to other non-steroidal anti-inflammatory drugs
7. Use in children.

8. Severe heart failure.
9. Use with concomitant NSAIDs including cyclooxygenase 2 specific inhibitors (see section 4.5).

#### 4.4 Special warnings and precautions for use

Undesirable effects may be minimized by using the minimum 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 should be regarded as an indication to discontinue therapy immediately.

The product should be used with caution in patients suffering from dehydration and renal dysfunction and in 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 at high 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 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).

##### 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 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. 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 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, 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.

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

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).

## **4.5 Interaction with other medicinal products and other forms of interaction**

Concurrent administration of other Plasma protein binding drugs, such as anticoagulants may require adjustment in their dosage.

**Anticoagulants:** NSAID may enhance the anticoagulant effect such as warfarin (see section 4.4). Concurrent administration of mefenamic acid with oral anti-coagulant 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 necessarily been associated with ponalgic:

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

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

*Antihypertensives:* 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 Aminoglycosides 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.

*Ciclosporin:* increased risk of nephrotoxicity with NSAID's.

*Corticosteroids:* increased 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.

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

*Methotrexate:* Decreased elimination of Methotrexate

*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 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:

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).

### Breast-feeding

Trace amounts of mefenamic acid may appear 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 (1/1000 to 1/100 ); rare(1/10,000 to 1/1000); very rare (1/10,000 ), not known (cannot be estimated from the available data).

#### Blood and the lymphatic system disorders:

Frequency not known: Haemolytic anaemia†, anaemia, hypoplasia bone marrow, haematocrit decreased, thrombocytopenic purpura, leukopenia with a risk of infection, sepsis, disseminated intravascular coagulation, , agranulocytosis, aplastic anaemia, eosinophilia, neutropenia, pancytopenia, thrombocytopenia.

† Haemolytic anaemia reversible when mefenamic acid is stopped. Reports are associated with 12 months of mefenamic acid therapy.

#### Immune system disorders:

Frequency not known: Hypersensitivity†, fixed drug eruption

† Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reaction and anaphylaxis, (b) respiratory tract reactivity or (c) assorted skin disorders

#### Metabolism and nutritional disorders:

Frequency not known: Glucose intolerance impaired† hyponatraemia.

† in diabetic patients

#### Psychiatric disorders:

Frequency not known: Confusion, depression, hallucinations, nervousness.

#### Nervous system disorders:

Frequency not known: Optic neuritis, headaches, paraesthesia, dizziness, drowsiness, meningitis aseptic† , blurred vision, convulsions, insomnia.

† 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).

#### Eye disorders:

Frequency not known: Eye irritation, colour blindness, visual impairment.

#### Ear and labyrinth disorders:

Frequency not known: Ear pain, tinnitus, vertigo.

#### Cardiac / Vascular disorders:

Frequency not known: Palpitations, dyspnoea, oedema, hypertension, hypotension and cardiac failure†

† 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)

#### Respiratory, thoracic and mediastinal disorders:

Frequency not known: Asthma, dyspnoea.

#### Gastrointestinal disorders:

Frequency not known: Peptic ulcer†, gastrointestinal perforation, gastrointestinal haemorrhage††, nausea, vomiting, diarrhoea†††, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, mouth ulceration, colitis, Crohn's disease (See section 4.4), gastritis, anorexia, enterocolitis, pancreatitis and steatorrhea.

† gastric ulceration with or without haemorrhage,

†† Gastrointestinal perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). 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.

††† 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.

#### Hepato-biliary disorders:

Frequency not known: liver function test abnormal, jaundice cholestatic, hepatotoxicity, hepatitis, hepatorenal syndrome.

Skin and subcutaneous tissue disorders:

Frequency not known: Angioedema, laryngeal oedema, erythema multiforme, face oedema, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, rash, photosensitivity reaction, pruritus and urticaria.

#### Renal and urinary disorders:

Frequency not known: glomerulonephritis, Tubulointerstitial nephritis, dysuria, haematuria, nephrotic syndrome, acute renal failure† proteinuria, renal failure including renal papillary necrosis.

† Non oliguric renal failure particularly in dehydration. 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.

#### General disorders and administration site conditions:

Frequency not known: Fatigue, malaise, multi-organ failure, pyrexia, hyperhydrosis.

Investigations:

Frequency not known: Total bile acids increased†

† 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: [www.hpra.ie](http://www.hpra.ie); E-mail: [medsafety@hpra.ie](mailto:medsafety@hpra.ie).

## **4.9 Overdose**

Gastric lavage in the conscious patients and intensive supportive therapy where necessary. Vital functions should be monitored and supported. Activated charcoal has shown to be a powerful adsorbent 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 involved daily dosages under 3g.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Mefenamic acid, an anthranilic acid derivative, is a non-steroidal agent with anti-inflammatory, analgesic and antipyretic properties. Its anti-inflammatory effect was first established in the UV erythema model of inflammation.

ATC code: M01AG01

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 (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 gastrointestinal tract. Mefenamic acid is extensively bound to plasma proteins. Peak levels of 10 mg/l occur two hours after the 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

No further relevant information other than that which is included in other sections of the Summary of Product Characteristics.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Microcrystalline cellulose  
Sodium Starch Glycollate Type A  
Gelatin  
Magnesium Stearate  
Croscarmellose Sodium  
Colloidal Anhydrous Silica

#### Film Coat

Lactose Monohydrate  
Hydroxypropylmethylcellulose (Hypromellose) E464  
Polyethylene glycol (Macrogol)  
Titanium Dioxide E171  
Iron oxide yellow E172  
Quinoline Yellow Aluminium Lake E104

### 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 container in order to protect from light

### 6.5 Nature and contents of container

Polypropylene containers with polypropylene tamper evident caps.

Pack sizes: 50, 100 and 168 capsules.

Not all pack sizes may be marketed

### 6.6 Special precautions for disposal and other handling

No special requirements for disposal.

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

## 7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals (Ireland) Ltd  
4045 Kingswood Road  
Citywest Business Park  
Co Dublin  
Ireland



**8 MARKETING AUTHORISATION NUMBER**

PA 0073/097/002

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 23<sup>rd</sup> October 1987

Date of last renewal: 23<sup>rd</sup> October 2007

**10 DATE OF REVISION OF THE TEXT**

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