

**IRISH MEDICINES BOARD ACTS 1995 AND 2006**

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

**(S.I. No.540 of 2007)**

**PA0282/048/002**

Case No: 2065827

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

**Norton Healthcare Limited T/A IVAX Pharmaceuticals UK**

**Regent House, 5-7 Broadhurst Gardens, Swiss Cottage, London NW6 3RZ, United Kingdom**

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

**Mefenamic Acid, 500 Milligram**

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 **19/05/2009**.

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 500 mg Film-Coated Tablets.

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Mefenamic Acid 500 mg.

Sunset yellow (E110) content of approximately 0.0625mg per tablet.

For excipients, see 6.1

#### 3 PHARMACEUTICAL FORM

Film-coated tablet.

Yellow, film-coated, ovoid tablets, about 18mm by 10mm, embossed 'MEF 500' on one face with a twin triangle logo on the reverse.

#### 4 CLINICAL PARTICULARS

##### 4.1 Therapeutic Indications

For the relief of mild to moderate pain associated with rheumatic muscular or arthritic disorders (including rheumatoid arthritis, and osteo-arthritis), trauma, headache, dental pain, post-operative or post-partum states.

In the management of dysfunctional menorrhoea and the pain of dysmenorrhagia.

##### 4.2 Posology and method of administration

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*).

##### 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.

##### Route of Administration:

Oral.

### 4.3 Contraindications

1. Use in patients with gastric and or intestinal ulceration or inflammation and in patients with inflammatory bowel disease.
2. Use in patients with renal or hepatic impairment.
3. Use in pregnancy or lactation.
4. Use in patients shown to be hypertensive to mefenamic acid, any of the other ingredients of this medication, aspirin or other non-steroidal anti-inflammatory drugs.

### 4.4 Special warnings and precautions for use

Undesirable effects may be reduced by using the minimum effective dose for the shortest possible duration. 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.

In dehydrated patients and 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.

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.

Mefenamic Acid should be used with caution in patients with a history of peptic ulceration or inflammatory bowel disease and in patients with cardiac impairment.

Caution in asthmatics. Some asthmatics may have their asthma symptoms triggered by non-steroidal anti-inflammatory drugs. Episodes triggered in this way can be quite severe and even life-threatening.

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

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

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

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

Concurrent administration with other protein bound drugs such as anticoagulants may require adjustment in their dosage. Concurrent administration of mefenamic acid with:

**It is considered unsafe to NSAIDs in combination with Warfarin or Heparin unless under direct medical supervision.**

The following interactions have been reported with NSAIDs but have not necessarily been associated with Mefenamic acid:

Antihypertensives and diuretics: a reduction in antihypertensive and diuretic effect has been observed. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

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

Lithium and methotrexate: elimination of these drugs can be reduced.

Ciclosporin: the risk of nephrotoxicity of ciclosporin may be increased with NSAIDs.

Corticosteroids: concomitant use may increase the risk of gastrointestinal ulceration or bleeding (*see section 4.4, Special warnings and precautions for use*).

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.

Other analgesics: concomitant use of two or more NSAIDs should be avoided.

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

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.

Some medicines of a similar type to mefenamic acid have found to interfere with mifepristone (a medicine used in the termination of pregnancy).

#### 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 not recommended.

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

	Common (>1%; <10%)	Uncommon (>0.1%; <1%)	Rare (>0.01%; <0.1%)	Very rare (<0.01%, including isolated reports)
Gastrointestinal	Diarrhoea, associated proctocolitis, serious gastrointestinal toxicity such as bleeding, ulceration, and perforation can occur at any time.		Nausea, vomiting, abdominal pain	

Skin and hair	Skin rashes		Stevens-Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis) and erythema multiforme. Facial oedema	
Nervous system			Headache, drowsiness, dizziness	
Liver and kidneys	Glomerulonephritis, acute interstitial nephritis with haematuria and Proteinuria and occasionally nephrotic syndrome.	Non-oliguric renal failure	Pancreatitis and cholestatic jaundice	
Blood		Thrombocytopenic purpura	Reversible haemolytic anaemia, temporary lowering of the white blood cell count, eosinophilia, agranulocytosis, pancytopenia and aplastic anaemia	
Cardiovascular			Palpitations, hypotension	
Respiratory and thoracic disorders		Bronchospasm and/or urticaria	Laryngeal oedema	
Senses			Abnormal vision	
Endocrine disorders			Glucose intolerance	
Immune system disorders			Anaphylaxis	

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 dose develop the drug should be withdrawn 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 withdraw medication. There have been rare reports of Stevens-Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis) and erythema multiforme.

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

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

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.

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, pancytopenia and aplastic anaemia have been reported. Blood studies should therefore be carried out during long term administration and the appearance of any dyscrasias is an indication to discontinue therapy.

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

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. Pancreatitis and cholestatic jaundice have also 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.

#### **4.9 Overdose**

Gastric lavage in the conscious patients and intensive supportive therapy where necessary. Vital function 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 lead 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 regimes adhered to since some reports have involved daily dosages under 3g.

### **5 PHARMACOLOGICAL PROPERTIES**

## 5.1 Pharmacodynamic properties

*ATC Code M01AG01.*

An anthranilic acid derivative.

## 5.2 Pharmacokinetic properties

It is absorbed rapidly after oral dosing and excreted both in urine and faeces with a half life of 2-4 hours.

## 5.3 Preclinical safety data

Not applicable.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Tablet core:

Microcrystalline cellulose  
Povidone K30  
Sodium starch glycolate (Type A)  
Magnesium stearate

Film coating:

Opadry OY 8494 yellow, containing hypromellose (E464), titanium dioxide (E171), Quinoline Yellow (E104), Sunset Yellow (E110) and 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

Polypropylene tubular tablet container with an open end equipped to accept a polyethylene closure with a tamper-evident tear strip and is the appropriate size to accommodate 50, 100, 250, 500 or 1000 tablets.

Blister packs of PVdC-coated PVC/Aluminium blisters (60g/m<sup>2</sup> PVdC on 250µm PVC/20 µm Al) in pack sizes of 7, 14, 28, 30, 50, 60, 84, 90, 100, 112, 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**

Norton Healthcare Ltd  
T/A IVAX Pharmaceuticals UK  
Regent House  
5-7 Broadhurst Gardens  
Swiss Cottage  
London, NW6 3RZ  
United Kingdom

## **8 MARKETING AUTHORISATION NUMBER**

PA 0282/048/002.

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

Date of first authorization: 02 January 1991.

Date of last renewal: 02 January 2006.

## **10 DATE OF REVISION OF THE TEXT**

February 2009