

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **Product Summary**

#### **1. TRADE NAME OF THE MEDICINAL PRODUCT**

Mefenamic Acid Tablets 500mg  
Meflam 500  
Opustan 500  
Contraflam

#### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 500mg of mefenamic acid

#### **3. PHARMACEUTICAL FORM**

Caplet shaped, yellow, film-coated tablets, embossed with Antigen logo'a' and 'MA500' on one side, intended for oral administration to human beings

#### **4. CLINICAL PARTICULARS**

##### **4.1 Therapeutic Indications**

1. As an anti-inflammatory analgesic for the symptomatic relief of rheumatoid arthritis (including Still's Disease), osteoarthritis and pain including muscular, traumatic and dental pain, headaches of most aetiology, post-operative and post-partum pain.
2. Primary dysmenorrhoea
3. Menorrhagia due to dysfunctional causes and presence of IUD when other pelvic pathology has been ruled out.

##### **4.2 POSOLOGY AND METHOD OF ADMINISTRATION**

**Adults** : The usual dosage is 500mg three times daily.

In menorrhagia to be administered on the first day of excessive bleeding and continued according to the judgement of the physician. In dysmenorrhoea to be administered at the onset of menstrual pain and continued according to the judgement of the physician.

**Elderly (over 65 years):** As for adults. Whilst no pharmacokinetic or clinical studies specific to the elderly have been undertaken, it has been used at normal dosage in trials which include many elderly patients.

However, it should be used with caution in elderly patients suffering from dehydration and renal failure. Non-oliguric renal failure and proctocolitis have been reported mainly in elderly patients who have not discontinued mefenamic acid after the development of diarrhoea.

The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

**Children:** Not Recommended For Children under 12 years.

For oral administration.

To be taken preferably with or after food.

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

### **4.3 Contraindications**

Hypersensitivity to mefenamic acid or to any of the excipients. Because the potential exists for cross-sensitivity to aspirin, ibuprofen, or other non-steroidal anti-inflammatory drugs, mefenamic acid must not be given to patients who have previously shown hypersensitivity reaction (e.g. asthma, bronchospasm, rhinitis, angioedema or urticaria) to these medicines.

Mefenamic acid is also contra-indicated in patients with inflammatory bowel disease, intestinal ulceration and 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).

Severe heart failure, hepatic failure and renal failure (see section 4.4).

During the last trimester of pregnancy (see section 4.6).

Treatment of pain after coronary artery bypass graft (CABG) surgery.

### **4.4 Special warnings and precautions for use**

Undesirable effects may be minimised by using the lowest 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 symptoms should be regarded as an indication to stop therapy immediately (see section 4.8).

Use with concomitant NSAIDs including cyclooxygenase 2 selective inhibitors (see section 4.5).

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

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

**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).

**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, Renal and Hepatic impairment:**

The administration of an NSAID may cause a dose dependant reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see also section 4.3).

**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).

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

**Gastrointestinal:**

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.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

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 the 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 the patient should not receive mefenamic acid again.

**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).

**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.

**Blood dyscrasias:**

Blood dyscrasias have been reported in association with mefenamic acid. Blood studies should be carried out during long term administration and the appearance of any dyscrasia is an indication to discontinue therapy.

**Liver function tests:**

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

**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 therapy with other plasma protein binding drugs may necessitate a modification in dosage.

Other analgesics including cyclooxygenase—2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (see section 4.4)

Care should be taken in patients treated with an NSAID and any of the following drugs, as interactions have been reported in some patients:

*Anticoagulants:* NSAIDs may enhance the anticoagulant effect such as warfarin (see section 4.4) and the dose of the anticoagulant may need to be reduced. 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.

The following interactions have been reported with NSAIDs but have not necessarily been associated with Contraflam Tablets:

*Lithium:* Decreased elimination of lithium and increased risk of lithium toxicity.

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

*Antihypertensives and diuretics:* a reduction in antihypertensive and diuretic effect has been observed. Diuretics can increase the 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 aminoglycoside and increased plasma concentrations.

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

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

*Corticosteroids:* Increased the risk of gastro-intestinal ulceration or bleeding (see section 4.4)

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

*Methotrexate*: elimination of the drug can be reduced, resulting in increased plasma levels.

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

*Probenecid*: reduction in metabolism and elimination of NSAIDs and metabolites.

*Quinolone antibiotics*: Animal data indicate that the 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

*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

## **4.6 Pregnancy and lactation**

Pregnancy:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, Mefenamic acid should not be given unless clearly necessary. If Mefenamic acid is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);

- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Mefenamic acid is contraindicated during the third trimester of pregnancy.

Lactation:

Trace amounts of mefenamic acid may be present in breast milk and transmitted to the nursing infant. Therefore, mefenamic acid should be prescribed with caution for nursing mothers.

See section 4.4 Special warnings and precautions for use, regarding female fertility.

#### **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**

*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, and gastrointestinal haemorrhage and exacerbation of colitis and Crohn's disease (See section 4.4) have been reported following administration. Less frequently, gastritis has been observed.

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.

Anorexia, colitis, enterocolitis, gastric ulceration with or without haemorrhage, pancreatitis, steatorrhea.

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:*

Borderline elevations of one or more liver function tests, cholestatic jaundice.

Mild hepatotoxicity, hepatitis, hepatorenal syndrome.

*Blood and the lymphatic system disorders:*

Haemolytic anaemia (reversible when mefenamic acid is stopped), 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.

Agranulocytosis, aplastic anaemia, eosinophilia, neutropenia, pancytopenia, thrombocytopenia.

*Immune system disorders:*

*Hypersensitivity:* Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reaction and anaphylaxis, (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea or (c) assorted skin disorders, including rashes of various types, pruritis, urticaria, purpura, angioedema and, more rarely exfoliative and, bullous dermatoses (including epidermal necrolysis and erythema multiforme).

*Metabolism and nutritional disorders:*

Glucose intolerance in diabetic patients, hyponatraemia.

*Psychiatric disorders:*

Confusion, depression, hallucinations, nervousness.

*Nervous system disorders:*

Optic neuritis, headaches, paraesthesia, dizziness, drowsiness, 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).

Blurred vision, convulsions, insomnia.

*Eye disorders:*

Eye irritation, reversible loss of colour vision, visual disturbances.

*Ear and labyrinth disorders:*

Ear pain, tinnitus, vertigo.

*Cardiac / Vascular disorders:*

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)

Palpitations.

Hypotension.

*Respiratory, thoracic and mediastinal disorders:*

Asthma, dyspnoea.

*Skin and subcutaneous tissue disorders:*

Angioedema, laryngeal oedema, erythema multiforme, face oedema, bullous reactions including Lyell's syndrome (toxic epidermal necrolysis) and Stevens-Johnson syndrome, perspiration, rash, photosensitivity reaction, pruritus and urticaria.

*Renal and urinary disorders:*

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:*

Fatigue, malaise, multi-organ failure, pyrexia.

*Investigations:*

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**

It is important that the recommended dose is not exceeded and the regime adhered to since some reports have involved daily dosages under 3g.

a) Symptoms

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma,

drowsiness, dizziness, tinnitus, fainting, occasionally convulsions. In cases of significant poisoning acute renal failure and liver damage are possible.

Mefenamic acid has a tendency to induce tonic-clonic (grand mal) convulsion in overdose.

b) Therapeutic measure

Patients should be treated symptomatically as required.

Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered.

Activated charcoal has been shown to be a powerful adsorbent for mefenamic acid and its metabolites. Studies in experimental animals and humans showed that a 5 to 1 ratio of charcoal to mefenamic acid resulted in considerable suppression of absorption of the drug. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose. Gastric lavage in the conscious patient and intensive supportive therapy where necessary.

Good urine output should be ensured.

Renal and liver function should be closely monitored.

Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

Frequent or prolonged convulsions should be treated with Intravenous diazepam. Other measures may be indicated by the patient's clinical condition.

Haemodialysis is of little value since mefenamic acid and its metabolites are firmly bound to plasma proteins.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Mefenamic acid is a non-steroidal anti-inflammatory agent with analgesic and anti-pyretic properties.

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**

Following oral administration, mefenamic acid is absorbed rapidly and is excreted both in urine and faeces, the half life in plasma is approximately 2 to 4 hours.

### *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 A3 hydroxymethyl derivative (metabolite I) and then A3 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 (Avicel pH 101)  
Sodium Starch Glycollate (Explotab)  
Gelatin  
Purified Water  
Magnesium Stearate  
Croscarmellose Sodium Type A. (Ac-di-Sol)  
Colloidal Silicon Dioxide. (Aerosil 200)  
Methanol  
Methylene Chloride  
Ethylcellulose (Ethocel 10 cps)  
Diethyl Phthalate  
Methylcellulose (Methocel E15)  
Opaspray Yellow K-I-6455

### **6.2. Incompatibilities**

Unknown.

### **6.3. Shelf Life**

Unopened : 3 years.  
After reconstitution: not applicable.  
After first opening: 3 years.

### **6.4. Special Precautions for Storage**

Store in a cool dry place.  
Protect from light and heat.

### **6.5. Nature and Contents of Container**

Polypropylene securitainers with tamper evident polypropylene caps.

Pack size: 50, 84, 100 and 168 tablets.

**6.6. Instructions for Use/Handling**

Use as directed by the physician.  
Keep out of reach of children.

**7. Marketing Authorisation Holder**

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**8. Marketing Authorisation Number**

PL 12762/0122

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13/03/2009

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