Ponstan Forte Tablets 500mg

1. NAME OF THE MEDICINAL PRODUCT
Ponstan™ Forte Tablets 500mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Mefenamic acid BP 500mg

3. PHARMACEUTICAL FORM
Yellow film coated tablet, inscribed 'Ponstan' on one side

4. CLINICAL PARTICULARS

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

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 an IUD when other pelvic pathology has been ruled out.

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)

For oral administration

Adults

1 tablet (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 with Ponstan, it has been used at normal dosage in trials which included many elderly patients.

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.

Ponstan should be used with caution in elderly patients suffering from dehydration and renal disease. Non-oliguric renal failure and proctocolitis have been reported mainly in elderly patients who have not discontinued Mefenamic Acid after the development of diarrhoea.

**Children**

It is recommended that children under 12 years of age should be given Ponstan Paediatric Suspension (50mg/5ml).

**Do not exceed the stated dose.**

Ponstan Forte tablets should be taken preferably with or after food.

**4.3 Contraindications**

Patients hypersensitive to mefenamic acid or any of the other ingredients.

Mefenamic acid is contra-indicated in inflammatory bowel disease and in patients suffering from active or previous peptic and/or intestinal ulceration or history of upper gastrointestinal bleeding or perforation related to previous NSAIDs therapy.

Severe heart failure, severe hepatic failure and severe renal failure (see section 4.4 - Special warnings and precautions for use).

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

During the last trimester of pregnancy (see section 4.6 - Pregnancy and lactation)

Use with concomitant NSAIDs including cyclooxygenase 2 specific inhibitors (see section 4.5 - Interactions).

**4.4 Special warnings and precautions for use**
In all patients: 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)

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 – Posology and administration)

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 dependent 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 – Contraindications).

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).

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.

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 gastrotoxicity or bleeding such as corticosteroids, or anticoagulants such as warfarin or anti-platelet agents
such as aspirin (see section 4.5 - Interactions).

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 (e.g. ulcerative colitis, Crohn's Disease) as these conditions may be exacerbated (see section 4.8 – Undesirable effects).

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 – Undesirable effects).

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 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.

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. In the case of anticoagulants the dose of the anticoagulant may need to be reduced. Concurrent administration of mefenamic acid with oral anticoagulant drugs requires careful prothrombin time monitoring.

The following interactions have been reported with NSAIDS but have not necessarily been associated with Ponstan Tablets:

Other analgesics: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (see section 4.3 – Contraindications).

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

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

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

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

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

Corticosteroids: Concomitant use may increase the risk of gastrointestinal bleeding. (see section 4.4 – Special warnings and precautions for use).

Quinolone antibiotics: Animal data indicates that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

4.6 Pregnancy and lactation

Pregnancy: Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern. In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of the ductus arteriosus), use in the last trimester of pregnancy is contraindicated. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child (see section 4.3 - Contraindications). NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Lactation: 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.

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, exacerbation of colitis and Crohn's disease have been reported following administration. Less frequently, gastritis has been observed. 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.

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.

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

Cardiovascular: 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).

Other less common adverse events:

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, neutropenia, 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.

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.

Neurological and special senses: visual disturbances, optic neuritis, headaches, paraesthesia, 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), depression, confusion, hallucinations, tinnitus, vertigo, dizziness, malaise, fatigue and drowsiness.

Photosensitivity reactions, 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.

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, tinnitus, fainting, occasionally convulsions (mefenamic acid has a tendency to induce tonic-clonic (grand-mal) convulsions in overdose). In cases of significant poisoning acute renal failure and liver damage are possible.

(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. Alternatively, in adults gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

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.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

ANIMAL MODELS

Mefenamic acid is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic properties.

Its anti-inflammatory effect was first established in the UV erythema model of inflammation. Further studies included inhibition of granulation tissue growth into subcutaneous cotton pellets in rats and carrageenin 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. Peak levels of 10mg/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.

**Elimination**

Fifty two percent of a dose is recovered from the urine, 6% as mfenamic 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 mfenamic acid decline with a half life of approximately two hours.

5.3 Preclinical safety data
Preclinical safety data does not add anything of further significance to the prescriber.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose, pregelatinised starch, maize starch, polyvidone, silicon dioxide, talc, magnesium stearate, croscarmellose sodium type A, sodium lauryl sulphate, purified water*, Opadry OY-LS-22808 (H.P.M.C.2910 15cps, lactose, polyethylene glycol 4000, vanillin, E104, E110, E171), Opaglos AG7350 (purified water, beeswax white, carnauba wax yellow, polysorbate 20, sorbic acid).

*not detectable

6.2 Incompatibilities
None Known

6.3 Shelf life
36 months for amber polystyrene bottle

48 months for blister and HDPE DUMA and polypropylene container

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of container
a) Aluminium foil/pvc blister pack in cardboard carton. Pack sizes: 100

b) HDPE DUMA and polypropylene container. Pack sizes: 100 and 500

c) Amber polystyrene bottle with a high density polyethylene anti-arthritic closure. Pack sizes: 6, 12, 84, 100 and 500.

6.6 Special precautions for disposal and other handling
Not applicable

7. MARKETING AUTHORISATION HOLDER
Chemidex Pharma Limited
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Crabtree Road
Egham
Surrey TW20 8RB
United Kingdom

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