Ponstan* Film Coated Tablets
(Mefenamic Acid)

1 NAME OF MEDICINAL PRODUCT

PONSTAN Film Coated Tablets 500 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Mefenamic acid

Mefenamic acid is available as:
Film Coated Tablets containing 500 mg mefenamic acid

3 PHARMACEUTICAL FORM

Tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Symptomatic treatment of mild to moderate:

- acute and chronic pain associated with rheumatic diseases
- muscle pain, pain in the vertebral column (e.g. vertebral disk problems)
- post-injury or postoperative pain, swelling or inflammation
- pain associated with primary dysmenorrhea

Ponstan film coated tablets 500 mg - to be used by adults and adolescents from 14 years.

4.2 Posology and Method of Administration

Ponstan should be used at the lowest effective dose for shortest possible time.

Posology
The usual dosage for adults and juveniles as of 14 years of age is 500 mg to a maximum 1500 mg mefenamic acid per day in multiple daily doses and depending on the severity of the disease. For children aged 10 years and older and juveniles aged 12-14 years capsules with 250 mg are available for use.

The daily dosages indicated above should not be exceeded.

For the treatment of primary dysmenorrhea Ponstan should be started with the onset of menstrual pain. There is no experience with the symptomatic treatment of primary dysmenorrhea in juveniles under 16 years of age.

Method of administration
For oral use.
Ponstan film coated tablets are swallowed whole with some fluid together with a meal.

Use in patients with hepatic and renal impairment

See sections **4.3 Contraindications** and **4.4 Special Warnings and Precautions for Use**

Use in the elderly (from 65 years on)
See section **4.4 Special Warnings and Precautions for Use**

4.3 Contraindications

- hypersensitivity to the active ingredient or any of the excipients of the product.
- in patients having experienced asthma, urticaria or allergic rhinitis after taking acetylsalicylic acid (like Aspirin) or other non-steroidal anti-inflammatory drugs (NSAIDs).
- in patients with haemorrhagic diathesis
- in patients with active ulcers or with chronic upper or lower gastrointestinal inflammation or with a history of such disorders
- in patients with history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy; active, or history of recurrent peptic ulcer/haemorrhage.
- in patients with a history of renal disease or with impaired renal function
- in patients with severe heart failure and hepatic dysfunction
- in patients with hematopoietic disorders
- treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG)
- the third trimester of pregnancy, because of risks of premature closure of the ductus arteriosus, and prolonged parturition.

4.4 Special Warnings and Precautions for Use

The use of mefenamic acid with concomitant systemic non-aspirin NSAIDs, including cyclooxygenase-2 (COX-2) inhibitors, should be avoided. Concomitant use of a systemic NSAID and another systemic NSAID may increase frequency of gastrointestinal ulcers and bleeding.

Cardiovascular effects
NSAIDs may cause an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. The relative increase of this risk appears to be similar in those with or without known CV disease or CV risk factors. However, patients with known CV disease or CV risk factors may be at greater risk in terms of absolute incidence, due to their increased rate at baseline. To minimize the potential risk for an adverse CV event in patients treated with mefenamic acid, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV toxicity and the steps to take if they occur (see section **4.3 Contraindications**).

Hypertension
As with all NSAIDs, mefenamic acid can lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events. NSAIDs, including mefenamic acid, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with mefenamic acid and throughout the course of therapy.

Patients with uncontrolled hypertension, existing ischemic heart disease, peripheral arterial occlusive disease and/or cerebrovascular disease should only be treated after having carefully weighed the benefits of treatment against the potential risks.

Similar evaluation should be done before initiating prolonged treatment of patients with cardiovascular risk factors (e.g. hypertension, hyperlipidaemia, diabetes, smoking).

Fluid retention and oedema
As with other medicinal products known to inhibit prostaglandin synthesis, fluid retention and oedema have been observed in some patients taking NSAIDs, including mefenamic acid. Therefore, mefenamic acid should be used with caution in patients with compromised cardiac function and other conditions predisposing to fluid retention.

Gastrointestinal effects
NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms.

The anticipated benefit of treatment with high doses (within the recommended dose range) should be in reasonable relationship with the potentially increased risk of gastrointestinal adverse effects. When gastrointestinal bleeding or ulceration occurs in patients receiving mefenamic acid, the treatment should be withdrawn.

Elderly patients are at greater risk for serious gastrointestinal events. Special caution with regard to gastrointestinal adverse effects is advised for treatment of elderly persons, patients with CV disease, patients with concomitant use of medicinal products known to increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants like warfarin, selective serotonin reuptake inhibitors (SSRIs) or platelet aggregation inhibitors like Aspirin (see section **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**), patients ingesting alcohol or patients with a history of gastrointestinal disease. In such patients combination therapy with gastroprotective agents should be considered. Any unusual abdominal complaints, in particular upon initiation of treatment, should be reported by the patient.

If persistent diarrhoea occurs, the dosage should be reduced or treatment temporarily suspended.

Use with oral anticoagulants
The concomitant use of NSAIDs, including mefenamic acid, with oral anticoagulants increases the risk of GI and non-GI bleeding and should be given with caution. Oral anticoagulants include warfarin/coumarin-type and novel oral anticoagulants (e.g. apixaban, dabigatran, rivaroxaban). Anticoagulation/INR should be monitored in patients taking a warfarin/coumarin-type anticoagulant (see section **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

Skin reactions
Serious skin reactions, some of them fatal, including drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs, including mefenamic acid. Patients appear to be at highest risk for these events early in the course of therapy, the onset of the event 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.

Other warnings
As with other prostaglandin inhibitors, there have been reports of acute interstitial nephritis with haematuria, proteinuria and rare cases of nephrotic syndrome.

Treatment with Ponstan should be discontinued upon signs of hepatic dysfunction or pathologic liver function tests during treatment.

In rare cases, Ponstan has been associated with serious liver injury.

There has been evidence that drugs inhibiting the synthesis of cyclooxygenase/prostaglandin may impair female fertility secondary to an effect on ovulation. This is reversible after discontinuation of treatment (see section **4.6 Fertility, Pregnancy and Lactation**).

Special caution is indicated in the treatment of dehydrated patients and those with epilepsy or severe hypertension.

This medicine contains less than 1 mmol sodium (23 mg) per film coated tablet, that is to say essentially 'sodium-free'.

Renal Effects
Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly.

Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced renal disease
No information is available from controlled clinical studies regarding the use of Ponstan in patients with advanced renal disease. Therefore, treatment with Ponstan is not recommended in these patients with advanced renal disease. If therapy must be initiated, close monitoring of the patient's renal function is advisable.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

- Mefenamic acid interferes with the anti-platelet effect of low-dose aspirin, and thus may interfere with aspirin's prophylactic treatment of CV disease.
- Mefenamic acid has been shown to displace warfarin from protein binding sites and may enhance the effects of oral anticoagulants. Therefore, concurrent use of mefenamic acid with oral anticoagulants requires regular monitoring of prothrombin time.
- Concurrent use of corticosteroids, platelet aggregation inhibitors and selective serotonin reuptake inhibitors (SSRIs) increases the risk of gastrointestinal bleeding
- Toxicity of methotrexate may be potentiated by concurrent use of Ponstan, especially in patients receiving high doses of methotrexate.
- Urine tests with the diazole tablet test may yield false-positive results for bile pigment.
- Nonsteroidal anti-inflammatory drugs such as mefenamic acid may increase lithium levels and reduce renal lithium clearance. Therefore, patients receiving concomitant lithium should be carefully monitored for any signs of lithium toxicity.
- Mefenamic acid may potentiate the hypoglycaemic effect of oral antidiabetics.
- Concurrent treatment with ACE inhibitors, angiotensin II antagonists and/or diuretics may be associated with an increased risk of renal damage, especially in patients with impaired renal function (e.g. dehydrated patients or elderly patients with compromised renal function). Patients should be carefully monitored for serum creatinine, urea and concentration because potential impairment of renal function including the possibility of acute renal failure, which is usually reversible cannot be excluded.
- Concurrent treatment with cyclosporine and tacrolimus may also be associated with an increased risk of renal damage.
- Concomitant use of other nonsteroidal anti-inflammatory drugs is not recommended as frequency of adverse effects may be increased.

- Concomitant use of quinolones (e.g. ciprofloxacin) may increase the risk of seizures.
- Ponstan may reduce the effectiveness of antihypertensives (diuretics, ACE inhibitors, angiotensin II antagonists, beta-blockers).

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryonal/foetal development. Epidemiological data suggest an increased risk of spontaneous abortion and cardiac malformation and gastroschisis following use of a prostaglandin synthesis inhibitor during early pregnancy. It has been suggested that this risk will increase with dosage and duration of treatment. Studies in animals have shown that administration of an inhibitor of prostaglandin synthesis will result in increased pre- and post-implantation losses and embryonal/foetal mortality.

Moreover, increased incidence of various malformations, including cardiovascular malformation has been reported in animals having received a prostaglandin synthesis inhibitor during organogenesis.

Published studies and post-marketing reports describe maternal Non-Steroidal Anti-Inflammatory Drug (NSAID) use at approximately 20 weeks gestation or later in pregnancy associated with foetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment or failure. NSAIDs were shown to cause significant reduction in foetal urine production prior to reduction of amniotic fluid volume. There have also been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction and renal impairment without oligohydramnios, some of which were irreversible, even after treatment discontinuation.

These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation.

Complications of prolonged oligohydramnios may for example, include limb contractures and delayed lung maturation. In some post-marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

Therefore, prostaglandin synthesis inhibitors should only be given during the first and second trimester of pregnancy, if strictly required. Mefenamic acid should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the foetus. If NSAIDs are being used by a woman trying to become pregnant or during the first or second trimester of pregnancy, the dose is used to keep as low as possible and the duration of treatment as short as possible.

From the 20th week of pregnancy onward, NSAIDs use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation.

Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to NSAIDs for several days from gestational Week 20 onward. Ponstan should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy prostaglandin synthesis inhibitors may expose
- the foetus to the following risks:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

- mother and child to the following risks at the final stage of pregnancy:
  - a potential prolongation of bleeding time, an effect of platelet aggregation inhibition that may occur even at very low doses;
  - inhibition of uterine contractions with resultant delay or prolongation of parturition.

Therefore, the use of mefenamic acid in pregnant women in the first or second trimester of pregnancy is not recommended and is contraindicated during the third trimester of pregnancy. Caution is recommended in prescribing mefenamic acid during the first and second trimesters of pregnancy, particularly from the middle to end of the second trimester of pregnancy (onset at approximately 20 weeks) due to possible foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment of failure.

If after careful consideration of the benefit-risk, NSAID treatment is considered necessary to be administered anywhere from the middle (onset at approximately 20 weeks) to the end of the second trimester of pregnancy, the use should be limited to the lowest effective dose and shortest duration possible. It is also recommended that ultrasound monitoring of amniotic fluid be considered if mefenamic acid treatment extends beyond 48 hours and that NSAIDs treatment be discontinued if oligohydramnios occurs, followed by appropriate medical follow up.

Breast-feeding
As mefenamic acid is excreted in breast milk, Ponstan should not be used while breast-feeding.

Fertility
As with other agents known to inhibit the synthesis of cyclooxygenase/prostaglandin, use of mefenamic acid may affect female fertility and is therefore not recommended in females attempting to conceive. For women having problems to conceive or undergoing assessment for infertility discontinuation of mefenamic acid should be considered.

4.7 Effects on Ability to Drive and Use Machines

The effect of mefenamic acid on the ability to drive and use machines has not been evaluated.

4.8 Undesirable Effects

The most frequently reported side effects involve the gastrointestinal tract. Peptic ulcers, perforation or bleeding, being potentially fatal, may occur, especially in elderly patients (see section **4.4 Special Warnings and Precautions for Use**). Nausea, vomiting, diarrhoea, flatulence, constipation, melena, hematemesis, ulcerative stomatitis and deterioration of colitis and Crohn's disease (see section **4.4 Special Warnings and Precautions for Use**) have been reported with the use of mefenamic acid. Gastritis has been reported less frequently.

Evaluation of adverse effects has been based on the following frequency definitions:
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 lymphatic system disorders
Common: Eosinophilia
Very rare: Autoimmune haemolytic anaemia*, decreased haematocrit, leukopenia, thrombocytopenic purpura, agranulocytosis, pancytopenia, aplastic anaemia and bone marrow aplasia
Not known: Platelet aggregation inhibition

Immune system disorders
Rare: Anaphylactic reactions with bronchospasm and decreased blood pressure progressing to shock may develop

Metabolism and nutrition disorders
Rare: Glucose intolerance in diabetic patients, hyponatremia
Not known: Fluid retention

Psychiatric disorders
Rare: Nervousness, depression

Nervous system disorders
Uncommon: Drowsiness
Rare: Aseptic meningitis, blurred vision, convulsions, dizziness, fatigue, headache and insomnia

Eye disorders
Rare: Visual disturbances, eye irritations, reversible loss of colour vision

Ear and labyrinth disorders
Rare: Ear pain, tinnitus

Cardiac disorders
Rare: Palpitation, heart failure

Vascular disorders
Rare: Hypotension, hypertension (see section 4.4 **Special Warnings and Precautions for Use**)

General disorders and administration site conditions
Not known: Oedema

Respiratory, thoracic and mediastinal disorders
Rare: Asthma, dyspnoea

Gastrointestinal disorders
Common: Dose-related diarrhoea is a common adverse effect for which dosage should be reduced. Some patients may require discontinuation of treatment.
Constipation, nausea with or without vomiting and abdominal pain
Uncommon: Anorexia, heartburn, flatulence, enterocolitis, colitis, gastrointestinal ulceration with or without bleeding or perforation
Rare: Steatorrhoea, pancreatitis
Not known: Gastrointestinal inflammation

Hepatobiliary disorders
Rare: Jaundice, hepatitis, hepatorenal syndrome, moderate hepatotoxicity, hepatic dysfunction

Skin and subcutaneous tissue disorders
Rare: Angioedema, larynx oedema, erythema multiforme, facial oedema, sweating, urticaria, skin rash, Lyell's syndrome (toxic epidermal necrolysis), Stevens-Johnson syndrome
Not known: Pruritus, dermatitis exfoliative

Renal and urinary disorders
Very rare: Dysuria, haematuria, renal failure including papillary necrosis, tubulointerstitial nephritis, renal dysfunction, sodium and water retention
Not known: Glomerulonephritis, nephrotic syndrome

Investigations
Not known: Urobilinogen urine (false-positive), liver function test abnormal

**Reports are associated with ≥12 months of mefenamic acid therapy and the anaemia is reversible with discontinuation of therapy.*

Paediatric population
General disorders and administration site conditions
Not known: Hypothermia

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.

4.9 Overdose

Overdose may be associated with epileptic seizures, renal failure, confusional state, vertigo, hallucinations, severe gastrointestinal and central nervous symptoms, skin rash, general bleeding tendency and unconsciousness.

Acute intervention: Induction of emesis, gastric lavage followed by the administration of activated charcoal and monitoring of vital functions and of water and electrolyte balance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Non-steroidal anti-inflammatories and anti-rheumatics, fenamates; **ATC-Code:** M01 AG01

Ponstan contains mefenamic acid as active ingredient, a compound showing analgesic, but also marked anti-inflammatory as well as antipyretic activity.

Ponstan primarily acts by inhibiting prostaglandin synthesis.

5.2 Pharmacokinetic Properties

Absorption
Mefenamic acid is rapidly absorbed from the gastrointestinal tract. Following administration of an oral dose of 1 g to adults, peak plasma levels occur in 1 to 4 hours, with a half-life of 2 hours. Plasma levels following multiple doses are proportional to dose. One gram of mefenamic acid administered four times daily produces peak blood levels of 20 μg/mL by the second day of administration.

Distribution

Mefenamic acid is bound to plasma proteins at more than 90%.

Biotransformation
Hepatic metabolization (conjugation, oxidation)

Elimination
Following a single oral dose elimination is predominantly by renal route (52% to 67%) as unchanged drug or one of two metabolites, but also by biliary route (20% to 25%).

5.3 Preclinical Safety Data

A study in rats given 10 times the human dose showed decreased fertility and delayed parturition. No foetal abnormalities were seen either in this study or in another study with dogs given 10 times the human dose.

As mefenamic acid shows good passage of the placenta and is excreted in breast milk, its use during pregnancy and lactation should be avoided. See also section **4.6 Fertility, Pregnancy and Lactation**.

Long-term animal studies of cancerogenic potential have not been conducted.

Mefenamic acid has not been subjected to extensive mutagenicity tests. Results of all studies conducted so far were negative.

6 PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities

Not applicable.

6.2 Shelf Life

Please refer to outer carton for expiry date.

6.3 Special Precautions for Storage

Please refer to outer carton for storage conditions.

Pfizer Corporation Hong Kong Limited
MAY 2024

Version approved: 12 JUN 2024