PONSTAN FORTE

Mefenamic acid

500 mg Film-Coated Tablets

Reference Market: Switzerland

AfME Markets using same as LPD: Saudi Arabia

SUMMARY OF PRODUCT CHARACTERISTICS

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events
Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use. Mefenamic acid is ucontraindicated in the setting of coronary artery bypass graft (CABG) surgery).

Gastrointestinal Bleeding, Ulceration, and Perforation
NSAIDs cause an increased risk of serious gastrointestinal (GI) 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 withoutwarning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.

1. NAME OF THE MEDICINAL PRODUCT

Ponstan Forte 500 mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg Mefenamic acid.
Excipient with known effect: Each film-coated tablet contains 0.2 mg sodium.
For the full list of excipients see Section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Acute and chronic pain, particularly pain associated with rheumatic disease, muscle pain, pain in the region of the spinal column (intervertebral disc conditions, shoulder/neck syndrome etc.), post-operative pain and pain following injury, as well as headache, toothache and earache (in particular, pain following dental extraction).
- Primary dysmenorrhoea.
- Dysfunctional or intrauterine device (IUD) caused hypermenorrhoea when organic pelvic pathology has been excluded.
- Ponstan Forte may also be used for simultaneous pain relief and lowering the temperature in flu-like illnesses. In addition, it is suitable for symptomatic treatment of other infectious diseases associated with fever, especially those localized in the upper respiratory tract.

4.2 Posology and method of administration

Posology

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.

In general, adults and children over the age of 14 years take 1 tablet (500mg) three times daily, together with food. The dose may be reduced or increased as required. Daily dosage should not exceed 2.0 g (= 4 tablets)

Method of administration
For oral use.

4.3. Contraindications

- Hypersensitivity to the active ingredient or one of the excipients (see « Composition»).
- History of bronchospasm, urticaria or allergy like symptoms after taking acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.
- Third trimester of pregnancy and lactation period (see « Pregnancy/Lactation»).
- Active peptic and/or duodenal ulcerations or gastrointestinal bleeding.
- Inflammatory bowel diseases like M. Crohn, Colitis ulzerosa.
- Severe hepatic impairment (cirrhosis of the liver and ascites).
- Severe renal impairment (creatinine clearance < 30 ml/min).
- Severe congestive heart failure (NYHA III-IV).
- Treatment of postoperative pain following coronary bypass surgery (or use of a heart-lung machine).

4.4 Warnings and Precautions for use

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms. Patients on prolonged therapy should be kept under regular surveillance with particular attention to liver dysfunction, rash, blood dyscrasias or development of diarrhea. Appearance of any of these symptoms should be regarded as an indication to stop therapy immediately.

Gastrointestinal effects

Gastrointestinal inflammations, ulcerations, bleeding or perforations may develop at any time during treatment with non-steroidal anti-inflammatory drugs (NSAIDs), be it COX-2-selective or not, even without warning symptoms or a history of such problems. In order to reduce this risk, the lowest effective dose should be taken for the shortest treatment period possible.

Patients most at risk of developing these types of GI complications with NSAIDs are the elderly, patients with cardiovascular disease, patients concomitantly taking antiplatelet drugs such as acetylsalicylic acid (refer to «Contraindications» and «Interactions»), patients ingesting alcohol, or patients with a prior history of gastrointestinal disease, such as ulceration, GI bleeding or inflammatory conditions. Therefore, Ponstan Forte should be used with caution in these patients.

The concomitant use of mefenamic acid with systemic NSAIDs, including selective COX-2 inhibitors, oral anticoagulants, corticosteroids or selective serotonin reuptake inhibitors (SSRIs) (see «Interactions») should be avoided due to the increased risk for gastrointestinal side effects.

When persistent diarrhoea GI bleeding or ulceration occurs in patients receiving mefenamic acid, the treatment should be discontinued

Cardiovascular effects

For certain selective COX-2 inhibitors, placebo-controlled studies have shown an increased risk of thrombotic cardio- and cerebrovascular complications. It is not yet known whether this risk is directly correlated with the COX-1/COX-2 selectivity of the individual NSAID, all NSAIDs may have a similar risk. As no comparable clinical study data are currently available for mefenamic acid at maximum doses and in long-term treatment, a similarly increased risk cannot be ruled out. Until relevant data become available, mefenamic acid should be used only after a careful benefit/risk analysis in patients with established ischaemic heart disease, cerebrovascular disease, peripheral arterial occlusive disease or with significant risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking). Likewise, in view of this risk, the lowest effective dose should be taken for the shortest treatment period possible.

The relative increase of the cardiovascular (CV) risk appears to be similar in patients with or without 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.

Renal effects

The renal effects of NSAIDs include fluid retention with oedema and/or hypertension. In patients with impaired cardiac function and other conditions that predispose to fluid retention, mefenamic acid should therefore only be used with caution. Caution is also required in patients concurrently using diuretics or ACE inhibitors or are otherwise at increased risk of hypovolaemia.

In rare cases, NSAIDs, including mefenamic acid, may cause interstitial nephritis, glomerulitis, papillary necrosis and the nephrotic syndrome. NSAIDs inhibit the synthesis of renal prostaglandin which plays a supportive role in the maintenance of renal perfusion in patients whose renal blood flow and blood volume are decreased. In these patients, administration of an NSAID may precipitate overt renal decompensation, which is typically followed by recovery to pretreatment state upon discontinuation of NSAID therapy. Patients at greatest risk of such a reaction are those with congestive heart failure, hepatic deficiency, nephrotic syndrome, overt renal disease and the elderly. Such patients should be carefully monitored while receiving NSAID therapy.

Skin reactions

Under treatment with NSAIDs, serious skin reactions, some of them with fatal outcome, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis (Lyell syndrome) drug eruption with eosinophilia and systemic symptoms (DRESS) and generalized bullous fixed drug eruption (GBFDE) have been reported very rarely (see «Undesirable effects»). The risk of occurrence of this reaction seems to be greatest at the start of treatment and these reactions are observed in most cases within one month of the start of treatment. Ponstan Forte should be discontinued at the first occurrence of skin rash, changes to the mucosa or any other sign of hypersensitivity reaction.

Haematological effects

Mefenamic acid, like other nonsteroidal anti inflammatory drugs, decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined. Patients suffering from clotting impairment should be carefully monitored.

During long-term treatment with Ponstan Forte, regular blood counts and renal function tests should be carried out. This applies particularly to patients with pre-existing impairment of renal function and to elderly patients.

Additional Remarks

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 «Pharmacokinetics»).

In patients with impaired liver function or epilepsy Ponstan Forte should also be administered with caution.

Excipients of particular interest

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

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, i.e. they are almost ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Acetylsalicylic acid
Mefenamic acid interferes with the anti-platelet effect of low-dose acetylsalicylic acid (ASS), and thus may interfere with ASS's prophylactic treatment of cardiovascular disease.

Hypoglycemic agents
There have been reports of changes in the effects of oral hypoglycemic agents in the presence of NSAIDs. Therefore, mefenamic acid should be administered with caution in patients receiving insulin or oral hypoglycemic agents.

Anticoagulants
Mefenamic acid has been shown to displace warfarin from protein binding sites and may enhance the response to oral anticoagulants. 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. This applies to anticoagulants of the warfarin-type as well as for novel oral anticoagulants (apixaban, dabigatran and, rivaroxaban). Anticoagulation should therefore be monitored in patients taking oral anticoagulants concomitantly with mefenamic acid.

Anti-hypertensives including diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists (AIIA) and beta-blockers
NSAIDs can reduce the efficacy of diuretics and other antihypertensive drugs.

In patients with impaired renal function (e.g. dehydrated patients or elderly patients with compromised renal function), co-administration of ACE inhibitors or AIIAs or diuretics with cyclo-oxygenase inhibitors can increase the deterioration of the renal function, including the possibility of acute renal failure, which is usually reversible. The occurrence of these interactions should be considered in patients taking mefenamic acid concomitantly with such anti-hypertensives.

Therefore, the concomitant administration of these drugs should be done with caution, especially in elderly patients. Patients should be adequately hydrated and the need to monitor the renal function should be assessed in the beginning of the concomitant treatment and periodically thereafter.

Cyclosporine
Because of their effect on renal prostaglandins, NSAIDS such as mefenamic acid may increase the risk of nephrotoxicity with cyclosporine.

Corticosteroids
Increased risk of gastrointestinal ulceration or bleeding.

Lithium
Mefenamic acid has produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. Thus, when mefenamic acid and lithium are administered concurrently, patients should be observed carefully for signs of lithium toxicity.

Methotrexate
Caution is advised when methotrexate is administered concurrently with NSAIDs, including mefenamic acid, because NSAID administration may result in increased plasma levels of methotrexate.

Selective Serotonin Reuptake Inhibitors (SSRIs)
The concomitant use of NSAIDs, including mefenamic acid, and SSRIs may increase the risk of gastrointestinal bleeding (see « Warnings and Precautions»).

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

Anti-platelet agents
Increased risk of gastrointestinal ulceration or bleeding.

4.6 Fertility, pregnancy and lactation

Pregnancy
Inhibition of prostaglandin synthesis may negatively influence pregnancy and/or embryo development. Data from epidemiological studies points to an elevated risk for miscarriage as well as for cardiac deformities and gastroschisis following use of prostaglandin synthesis inhibitors in early pregnancy. It is supposed that this risk may increase with dose and duration of therapy.
It has been demonstrated in animals that application of prostaglandin synthesis inhibitors causes pre- and post-implant loss and embryo-fetal lethality. Moreover, increased incidence of various deformities including cardiovascular deformities, have been observed in animals which received prostaglandin synthesis inhibitors during organogenesis.

During the first and second trimester of pregnancy Ponstan Forte should be used only if absolutely necessary and particularly avoided after 20 weeks or later of pregnancy. It may cause rare but serious kidney problems in an unborn baby. This can lead to low levels of amniotic fluid surrounding the baby and possible complications. In case Ponstan Forte is used in women trying to become pregnant, or during the first and second trimester of pregnancy doses should be kept as low and duration of therapy as short as possible. The health care professionals should consider ultrasound monitoring of amniotic fluid if NSAID treatment extends beyond 48 hours and discontinue the NSAID if oligohydramnios is found.

Oligohydramnios/neonatal renal insufficiency/constriction of the ductus arteriosus
Taking NSAIDs in the 20th week of pregnancy or later may cause fetal renal function disorders, oligohydramnios and in certain cases neonatal renal insufficiency. These undesirable effects occur on average after days or weeks of treatment, although in rare cases oligohydramnios has already been reported 48 h after the start of NSAID treatment. Oligohydramnios is often, but not always, reversible by cessation of the treatment. Complications of prolonged oligohydramnios may include e.g. contractures of the limbs and retarded maturation of the lungs. After introduction onto the market, invasive procedures such as exchange transfusion or dialysis had to be performed in some cases of limited neonatal renal function.

In addition, a constriction of the ductus arteriosus after treatment in the second trimester has been reported, but was reversed again in most cases after treatment ceased.

Consider ultrasound monitoring of the amniotic fluid and fetus heart if treatment with Ponstan Forte lasts for more than 48 h.

Cease administration of Ponstan Forte if oligohydramnios or constriction of the ductus arteriosus occurs and perform a subsequent examination consistent with clinical practice.

The use of Ponstan Forte is contraindicated in the third trimester of pregnancy. All prostaglandin synthesis inhibitors may
- expose the fetus to the following risks:
    - Cardio-pulmonary toxicity (connected with the premature closure of the ductus arteriosus and pulmonary arterial hypertension);
    - Renal dysfunction that may progress to renal failure with oligohydramniosis.
- expose mother and child to the following risks:
    - Potential prolongation of bleeding time, this thrombocyte aggregation inhibiting effect might even occur at very low doses;
    - Inhibition of uterus contractions with the consequence of late onset of or prolonged labour.

Lactation
Because mefenamic acid passes into breast milk with associated possible adverse effects on the child, nursing mothers should not use Ponstan Forte.

Fertility
The use of mefenamic acid may influence female fertility, and is therefore not recommended in women wishing to become pregnant. Women with difficulties in becoming pregnant or those undergoing infertility check-ups the 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 or use machinery has not been systematically evaluated. Due to potential adverse side-effects like dizziness and fatigue caution is generally advised.

4.8 Undesirable effects

Side effects are classified according to organ class and incidence, and are defined as follows: «very common» (≥1/10); «common» (≥1/100, <1/10); «uncommon» (≥1/1000, <1/100); «rare» (≥1/10'000, <1/1000); «very rare» (≤1/10'000); «not known»: spontaneous reporting from post-marketing surveillance.

Blood and lymphatic system disorders
Very rare: Changes in blood counts (leucopenia, autoimmune haemolytic anaemia, aplastic anaemia, agranulocytosis, purpura, eosinophilia, thrombocytopenia, pancytopenia, bone marrow aplasia, decreased hematocrit).
Not known: Platelet aggregation inhibition.

Immune system disorders
Rare: Allergic manifestations such as allergic oedema, bronchospasm and anaphylactic reactions, see also SOC «Skin and subcutaneous tissue disorders».

Metabolism and nutrition disorders
Rare: Glucose intolerance in diabetic patients, hyponatremia.

Nervous system disorders
Rare: Headaches, drowsiness, dizziness, fatigue, nervousness, depression, insomnia, convulsions, aseptic meningitis.

Eye disorders
Rare: Visual disturbances (blurred vision), eye irritations, reversible loss of color vision.

Ear and labyrinth disorders
Rare: Ear pain, tinnitus.

Cardiac disorders
Rare: Palpitations, heart failure.

Vascular disorders
Rare: Hypotension, hypertension.

Respiratory, thoracic and mediastinal disorders
Rare: Dyspnea, asthma.

Gastrointestinal disorders
The most frequently reported side effects associated with mefenamic acid involve the gastrointestinal tract.
Common: Diarrhoea, abdominal pain, nausea, vomiting.
Uncommon: Anorexia, colitis, constipation, enterocolitis, flatulence, gastrointestinal ulceration (with or without haemorrhage and perforation in isolated cases), pyrosis.
Rare: Pancreatitis, steatorrhoea.
Not known: Gastrointestinal inflammation.

Hepatobiliary disorders
Rare: Jaundice, hepatitis, hepatorenal syndrome, moderate hepatoxicity, hepatic dysfuntion.

Skin and subcutaneous tissue disorders

Uncommon: Perspiration, urticaria, pruritus, rash.
Rare: Angioedema, larynx edema, facial edema.
Very rare: Stevens-Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis), erythema multiforme.
Not known: Dermatitis exfoliative., drug eruption with eosinophilia and systemic symptoms (DRESS), generalized bullous fixed drug eruption (GBFDE).

Renal and urinary tract disorders
Very rare: Dysuria, renal failure including papillary necrosis, acute interstitial nephritis with hematuria and/or proteinuria, renal dysfunction, sodium and fluid retention.
Not known: Glomerulonephritis, nephrotic syndrome.

Investigations
Determination of urobilinogen in the urine using the azo method may give false positive results after a dose of mefenamic acid.

General disorders
Not known: Hypothermia (in pediatric patients).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after marketing 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 according to their local country requirements.

To Report side effects

- **Saudi Arabia**

National Pharmacovigilance Centre (NPC) • Call Center: 19999 • E-mail: npc.drug@sfda.gov.sa • Website: https://ade.sfda.gov.sa/

- **Other GCC States**

- *Please contact the relevant competent authority.*

4.9 Overdose

Signs and symptoms
Seizures, acute renal failure, coma, confusional state, vertigo, and hallucination have been reported with mefenamic acid overdoses. Overdose has led to fatalities.

Treatment:
Patients should be managed by symptomatic and supportive care following a mefenamic acid overdose. There are no specific antidotes. Following acute overdosage, induced emesis, and/or gastric lavage, and/or administration of activated charcoal may be considered dependent upon amount ingested and time since ingestion. Vital functions should be monitored and supported.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and anti- rheumatic products, non-steroids, fenamates
ATC-Code: M01AG01

Mechanism of action:
Ponstan Forte contains the active ingredient mefenamic acid, a non-steroidal anti-inflammatory drug, which has anti-inflammatory and antipyretic effects in addition to its analgesic properties. Mefenamic acid acts mainly through the inhibition of prostaglandin synthesis.

5.2 Pharmacokinetics

Absorption
Mefenamic acid is rapidly absorbed following an oral dose. Absorption is more than 70%. Peak plasma concentrations are measured 1-3 h after administration. The course of the plasma concentration shows linearity with the dose.

Distribution
Mefenamic acid is more than 90% bound to plasma proteins and is able to cross the placental barrier. Less than 1% of the serum concentration is found in breast milk.

Metabolism
Mefenamic acid metabolism is predominantly mediated via cytochrome P450 CYP2C9 in the liver. Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates should be administered mefenamic acid with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

The substance undergoes intensive biotransformation. The main metabolites are the 3-hydroxymethyl and the 3-carboxyl derivatives. Both these metabolites are partially conjugated to glucuronides and show only weak analgesic and anti-inflammatory effects.

Elimination
The plasma half-life is about 2 h. Excretion of the mefenamic acid metabolites is primarily in the urine. The proportion of free mefenamic acid in the urine is less than 5%.

5.3 Preclinical safety data

Mutagenicity
Mefenamic acid was not extensively investigated with regard to mutagenicity. Hitherto studies were negative.

Carcinogenicity
Long-term studies in animals of a tumorigenic potential are not available.

Reproductive and developmental toxicity
Animal experiments showed no evidence of teratogenic properties. Mefenamic acid penetrates the placenta and reaches in the plasma of monkey fetuses comparable values as in the plasma of the mother. Because of the mechanism of action, there may be an inhibition of labor, premature closure of the ductus arteriosus Botalli (in particular upon exposure after the 33rd week of pregnancy) and an increased bleeding tendency in mother and child.
Theoretically, there is the possibility of renal dysfunction of the fetus.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose, Maize Starch, Methylcellulose, Sodium Lauryl Sulphate, Colloidal Anhydrous Silica, Magnesium Stearate, Talc, Titanium Dioxide (E171), Hypromellose, Macrogol 6000, Iron Oxide Yellow (E 172), and Vanillin

6.2 Incompatibilities

NA

6.3 Shelf life

Do not use Ponstan forte after the expiry date which is stated on the carton after EXP:. The expiry date refers to the last day of that month.

Shelf life 36 months.

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

Pale yellow, oval, biconvex, film-coated tablet, debossed with "500" on one side.
Pack size: 20 Film-coated tablets.

6.6 Special precautions for disposal and handling

Keep out of the sight and reach of children.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. FURTHER INFORMATION

Marketing Authorization holder and Manufactuer:
Pfizer Manufacturing Deutshland GmbH, Betriebsstatte Freiburg, Germany

8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01-Jan-1981

9. DATE OF LAST REVISION OF THE TEXT

December 2023.