PONSTAN FORTE ®

Film Coated Tablets 500 gm

Mefenamic acid

Reference Market: Switzerland

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ponstan Forte®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition

Active substances: Mefenamic acid.

Excipients with known effect*:*

Sodium content per film-coated tablet: 0.2 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pharmaceutical form and active substance quantity per unit

1 film-coated tablet contains 500 mg of mefenamic acid. Pale yellow, oval, biconvex film-coated tablet debossed with "500" on one side.

4. Clinical particulars

4.1 Therapeutic indications

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

Dosage/Administration

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

Usual dosage

Ponstan Forte film-coated tablets In general, adults and children over the age of 14 years take 1 tablet of Ponstan Forte 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).

Special dosage instructions

Children and adolescents

Children should receive mefenamic acid treatment for short term only, unless treated for Still's disease.

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

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[1] 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

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.

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 «Pharmacokinetic »).

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

Excipients of particular interest

Film-coated tablets contain less than 1 mmol sodium (23 mg) per each film-coated tablet, i.e. they are almost «sodium-free».

4.5 Interaction with other medicinal products and other forms of interaction

Interactions

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.
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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.

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 mefenamic acid should be used only if absolutely necessary. In case mefenamic acid 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 use of mefenamic acid 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 oligohydramnios.
- 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

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.

Renal and urinary tract

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.

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 very 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.

4.9 Overdose

Generalised convulsions or muscle twitching may occur with an overdose. These respond to diazepam given intravenously.

Acute renal failure and coma have also been reported. Treatment: emptying the stomach by gastric lavage or induced vomiting and subsequent administration of activated charcoal, with close observation of the patient's vital signs.

Haemodialysis is of little use, because of the high protein binding of mefenamic acid and its metabolites.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Properties/Effects

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.

Pharmacodynamics

See «Mechanism of action».

Clinical efficacy

No information provided.

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 CYP 2C9 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.[3]

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 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 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

Film-coated tablet: Cellulosum microcristallinum, maydis amylum, methylcellulosum, natrii laurylsulfas, silica colloidalis, magnesii stearas, talcum, hypromellosum, polyethylenglycolum 6000, Color: titanii dioxidum (E171), ferrum oxydatum flavum (E172), arom.: vanillinum.

6.2 Incompatibilities

Effects on diagnostic methods

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

6.3 Shelf life

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

6.4 Special precautions for storage

Store below 30°C in a dry place.

6.5 Nature and contents of container

Film-coated tablets 500 mg: 10, 20, 30, 50, 100.

Not all pack sizes or presentations may be marketed.

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 authorisation holder:

Pfizer AG

Schärenmoosstrasse 99

8052 Zürich, Switzerland

Manufcaturer, Packaging and Release:

Pfizer Manufacturing Deutshland GmbH, Betriebsstätte Freiburg, Germany

Date of last revision

July 2020

THIS IS A MEDICAMENT

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the Pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep all medicaments out of reach and sight of children

Council of Arab Health Ministers
Union of Arabic Pharmacists