PONSTAN®
(Mefenamic Acid)

1. NAME OF THE MEDICINAL PRODUCT

Ponstan®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Mefenamic Acid.

3. PHARMACEUTICAL FORM

Ponstan® Tablets 250mg.

Pharmaceutical form and active substance quantity per unit
Tablet: 1 tablet contains 250 mg of mefenamic acid. Off-white Round flat faced beveled edge, double scored on one side and P-D on the other side.

Ponstan® Forte Tablets 500mg.

Pharmaceutical form and active substance quantity per unit
Tablet:1 tablet contains 500 mg of mefenamic acid. Light yellow to yellow Elliptical biconvex, one side is plain & other side is engraved with "Ponstan Forte"

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 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

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

Usual dosage
Ponstan tablets: In general, adults and children over the age of 14 years take 1 tablet of Ponstan 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 of 500mg and 8 tablets of 250 mg).

4.3. CONTRAINDICATIONS

- Hypersensitivity to the active ingredient or one of the excipients (see section 6.1. LIST OF EXCIPIENTS).
- 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 section 4.6. FERTILITY, PREGNANCY AND 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. SPECIAL 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 acetylsalicylic acid (see 4.3. CONTRAINDICATIONS and 4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION), patients ingesting alcohol, or patients with a prior history of gastrointestinal disease, such as ulceration, GI bleeding or inflammatory conditions. Therefore, Ponstan 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 section 4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION) 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's syndrome), as well as drug eruption with eosinophilia and systemic symptoms (DRESS) have been reported very rarely (see section 4.8. 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 should be discontinued at the first occurence 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, 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 section 5. PHARMACOLOGICAL PROPERTIES).

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

Excipients of particular interest

Ponstan and Ponstan Forte Tablets contain less than 1 mmol sodium (23 mg) per each 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 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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

4.6. FERTILITY, PREGNANCY AND LACTATION

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.

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 should be used only if absolutely necessary. In case Ponstan 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.

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 lasts for more than 48 h.

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

The use of Ponstan 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.

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 "*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, drug eruption with eosinophilia and systemic symptoms (DRESS)

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).

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.

Reporting suspected adverse reactions
Reporting suspected adverse reactions after 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

ATC code: M01AG01.

Mechanism of action
Ponstan 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.

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 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.

Other information

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. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Excipients

Ponstan® Tablets 250mg:
Croscarmellose sodium, Lactose EP-NF sprayed dried, Microcrystalline Cellulose M-102, Stearic Acid Powder.

Ponstan® Forte Tablets 500mg:
Sodium Lauryl Sulphate, Polyvinylpyrollidone (Povidone USP), Isopropyl Alcohol, Vanillin, Corn Starch, FD & C Yellow No. 5 Al. Lake, Silicon Dioxide Colloidal, Micrcrystalline Cellulose, Magnesium Stearate.

Ponstan® and Ponstan® Forte Tablets contain less than 1 mmol sodium (23 mg) per each tablet.

6.2. INCOMPATIBILITIES

Not applicable.

6.3. SHELF LIFE

Ponstan® Tablets 250mg:

Pack (Nature & Content of Container)	Shelf-life	Storage Conditions
Blisters pack, 600 tablets per blister	60 months	Store at room temperature or below 30 C. Avoid exposure to heat and sunlight. Keep in a dry place.

Ponstan® Forte Tablets 500mg:

Pack (Nature & Content of Container)	Shelf-life	Storage Conditions
Blisters pack, 200 tablets per blister	60 months	Store at room temperature or below 30 C. Avoid exposure to heat and sunlight. Keep in a dry place.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store at room temperature or below 30°C.
Keep out of the reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER

Blister packs containing Tablets.

Ponstan® Tablets 250mg:
Each pack contains 600 tablets in 60 blisters.

Ponstan® Forte Tablets 500mg
Each pack contains 200 tablets in 20 blisters.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

None.

6.7. DRUG PRODUCT SPECIFICATIONS

Pfizer Specs.

7. MARKETING AUTHORISATION HOLDER

Marketed by:
Pfizer Pakistan Limited
B-2, S.I.T.E., Karachi, Pakistan

7.1 Manufacturer

Name of Manufacturing site	Address of site	Manufacturing step (if applicable)
Pfizer Pakistan Limited	B-2, S.I.T.E., Karachi, Pakistan	Manufacturing, Packaging, Testing & Batch Release

8. MARKETING AUTHORISATION NUMBER

Ponstan® Tablets 250 mg: 000130

Ponstan® Forte Tablets 500mg: 006978

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Ponstan® Tablets 250 mg:
Date of first Registration / Market Authorization: i.e., 24th April 1976
Date of latest renewal: i.e., 27th May 2021

Ponstan® Forte Tablets 500mg:
Date of first Registration / Market Authorization: i.e., 9th October 1983
Date of latest renewal: i.e., 27th May 2021

10. DATE OF REVISION OF THE TEXT

December 2023

Ponstan/LPD/PK-01
According to Switzerland Approved SmPC dated: 23-December-2022 & approved information in Pakistan

Marketed by:
Pfizer Pakistan Limited

*Please visit our website **www.pfizerpro.com.pk** for latest version of Product leaflet.*