

Ponstan®

Mefenamic acid

Capsule, Tablet

CDS

AfME markets using same as LPD: Ghana, Kenya, Nigeria

1. NAME OF THE MEDICINAL PRODUCT

PONSTAN®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: Mefenamic acid

Mefenamic acid is available as:

Capsules containing 250 mg, mefenamic acid
Coated Tablets containing 500 mg mefenamic acid

3. PHARMACEUTICAL FORM

Capsule, Tablet

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Mefenamic acid is indicated for:

The symptomatic relief of rheumatoid arthritis (including Still's Disease), osteoarthritis, and pain including muscular, traumatic, and dental pain, headaches of most etiology, post-operative, and postpartum pain.

The symptomatic relief of primary dysmenorrhea.

Menorrhagia due to dysfunctional causes or the presence of an intrauterine device (IUD) when organic pelvic pathology has been excluded.

Premenstrual syndrome.

The relief of pyrexia in pediatric patients over 6 months of age.

4.2. Posology and method of administration

Undesirable effects may be minimized by using the minimum effective dose for the shortest duration necessary to control symptoms.

The oral dosage form of mefenamic acid may be taken with food if gastrointestinal upset occurs.

Mild to moderate pain/rheumatoid arthritis/osteoarthritis in adults and adolescents over 14 years of age: 500 mg three times daily.

Dysmenorrhea: 500 mg three times daily, to be administered at the onset of menstrual pain and continued while symptoms persist according to the judgement of the physician.

Menorrhagia: 500 mg three times daily, starting with the onset of bleeding and associated symptoms and continued according to the judgement of the physician.

Premenstrual syndrome: 500 mg three times daily, starting with the onset of symptoms and continued until the anticipated cessation of symptoms according to the judgement of the physician.

For Still's Disease or antipyretic action in infants and children over 6 months to 14 years:
19.5 mg/kg to 25 mg/kg of body weight daily in divided doses three times daily.

Pediatric use

Mefenamic acid is reported to be effective for pyrexia in pediatric patients over 6 months of age, and for pain in adolescents over 14 years of age.

Use in the Elderly

Impairment of renal function, sometimes leading to acute renal failure, has been reported. Elderly or debilitated patients seem unable to tolerate ulceration or bleeding as well as some other individuals; most spontaneous reports of fatal gastrointestinal events are in this patient population. (see section 4.4 *Special warnings and precautions for use, Gastrointestinal (GI) Effects*).

4.3. Contraindications

Mefenamic acid should not be used in patients with known hypersensitivity to mefenamic acid or any of the components of this product.

Because the potential exists for cross-sensitivity to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs), mefenamic acid should not be given to patients in whom these drugs induce symptoms of bronchospasm, allergic rhinitis, or urticaria.

Mefenamic acid is contraindicated in patients with active ulceration or chronic inflammation of either the upper or lower gastrointestinal tract and should be avoided in patients with pre-existing renal disease.

Treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

Patients with severe renal and hepatic failure.

Patients with severe heart failure.

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 CV 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.

Fluid Retention and Edema

As with other drugs known to inhibit prostaglandin synthesis, fluid retention and edema 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, or worsened by, fluid retention. Patients with pre-existing congestive heart failure or hypertension should be closely monitored.

Gastrointestinal (GI) effects

If diarrhea occurs, the dosage should be reduced or temporarily suspended. Symptoms may recur in certain patients following subsequent exposure.

NSAIDs, including mefenamic acid, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. When GI bleeding or ulceration occurs in patients receiving mefenamic acid, the treatment should be withdrawn. Patients most at risk of developing these types of GI complications with NSAIDs are the elderly, patients with CV disease, patients using concomitant corticosteroids, antiplatelet drugs (such as aspirin), selective serotonin reuptake inhibitors, patients ingesting alcohol or patients with a prior history of, or active, gastrointestinal disease, such as ulceration, GI bleeding or inflammatory conditions Therefore, mefenamic acid should be used with caution in these patients (see section 4.3 *Contraindications*).

Skin reactions

Serious skin reactions, some of them fatal, including drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and generalized bullous fixed drug eruption (GBFDE) 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.

Laboratory tests

A false-positive reaction for urinary bile, using the diazo tablet test, may result following mefenamic acid administration. If biliuria is suspected, other diagnostic procedures, such as the Harrison spot test, should be performed.

Renal effects

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, liver cirrhosis, nephrotic syndrome, overt renal disease, and the elderly. Such patients should be carefully monitored while receiving NSAID therapy.

Discontinuation of NSAID therapy is typically followed by recovery to the pre-treatment state. Since mefenamic acid metabolites are eliminated primarily by the kidneys, the drug should not be administered to patients with significantly impaired renal function.

Hematologic effects

Mefenamic acid can inhibit platelet aggregation and may prolong prothrombin time in patients on warfarin therapy. (see section 4.5 *Interactions with other medicinal products and other forms of interaction*)

Hepatic effects

Borderline elevations of one or more liver function tests may occur in some patients receiving mefenamic acid therapy. These elevations may progress, may remain essentially unchanged, or may be transient with continued therapy. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with mefenamic acid. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, mefenamic acid should be discontinued.

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 Interactions with other medicinal products and other forms of interactions*).

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 aspirin, and thus may interfere with aspirin's prophylactic treatment of CV disease.

Anticoagulants: Mefenamic acid has been shown to displace warfarin from protein binding sites, and may enhance the response to oral anticoagulants. Therefore, concurrent administration of mefenamic acid with oral anticoagulant drugs requires frequent prothrombin time monitoring.

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, including ACE inhibitors, AIIA, and beta-blockers.

In patients with impaired renal function (e.g., dehydrated patients or elderly patients with compromised renal function), the co-administration of an ACE inhibitor or an AIIA and/or diuretics with a cyclo-oxygenase inhibitor 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 with an ACE inhibitor or an AIIA and/or diuretics.

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.

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding.

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

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.

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, especially in patients receiving high doses of methotrexate.

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

4.6. Fertility, pregnancy, and lactation

Fertility

Based on the mechanism of action, the use of NSAIDs may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. In women who

have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of NSAIDs, including mefenamic acid should be considered.

Pregnancy (see section 5.3 *Preclinical safety data*)

Since there are no adequate and well-controlled studies in pregnant women, this drug should be used only if the potential benefits to the mother justify the possible risks to the fetus. It is not known if mefenamic acid or its metabolites cross the placenta. However, because of the effects of drugs in this class (i.e., inhibitors of prostaglandin synthesis) on the fetal CV system (e.g., premature closure of the ductus arteriosus), the use of mefenamic acid in pregnant women is not recommended and should be avoided during the third trimester of pregnancy. Mefenamic acid inhibits prostaglandin synthesis which may result in prolongation of pregnancy and interference with labor when administered late in the pregnancy. Women on mefenamic acid therapy should consult their physician if they decide to become pregnant.

Inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from epidemiological studies suggest an increased risk of spontaneous abortion after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss.

If used during second or third trimester of pregnancy, NSAIDs may cause fetal renal dysfunction which may result in reduction of amniotic fluid volume or oligohydramnios in severe cases. Such effects may occur shortly after treatment initiation and are usually reversible upon discontinuation. Pregnant women on mefenamic acid should be closely monitored for amniotic fluid volume.

Lactation

Trace amounts of mefenamic acid may be present in breast milk and transmitted to the nursing infant. Therefore, mefenamic acid should not be taken by nursing mothers.

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.

4.8. Undesirable effects

Blood and lymphatic system disorders: agranulocytosis, aplastic anemia, autoimmune hemolytic anemia*, bone marrow hypoplasia, decreased hematocrit, eosinophilia, leukopenia, pancytopenia, thrombocytopenic purpura, platelet aggregation inhibition

Immune system disorders: anaphylaxis

Metabolism and nutrition disorders: glucose intolerance in diabetic patients, hyponatremia, fluid retention

Psychiatric disorders: nervousness

Nervous system disorders: aseptic meningitis, blurred vision, convulsions, dizziness, drowsiness, headache, and insomnia

Eye disorders: eye irritation, reversible loss of color vision

Ear and labyrinth disorders: ear pain

Cardiac disorders: palpitation

Vascular disorders: hypotension, hypertension

Respiratory, thoracic, and mediastinal disorders: asthma, dyspnea

Gastrointestinal disorders: gastrointestinal inflammation, gastrointestinal hemorrhage, gastrointestinal ulcer, gastrointestinal perforation

The most frequently reported side effects associated with mefenamic acid involve the gastrointestinal tract. Diarrhea appears to be the most common side effect and is usually dose-related. It generally subsides on dosage reduction, and rapidly disappears on termination of therapy. Some patients may not be able to continue therapy.

The following are the most common gastrointestinal side effects: abdominal pain, diarrhea, and nausea with or without vomiting.

Less frequently reported gastrointestinal/hepatobiliary side effects include: anorexia, cholestatic jaundice, colitis, constipation, enterocolitis, flatulence, gastric ulceration with and without hemorrhage, mild hepatic toxicity, hepatitis, hepatorenal syndrome, pyrosis, pancreatitis, and steatorrhea.

Skin and subcutaneous tissue disorders: angioedema, edema of the larynx, erythema multiforme, facial edema, Lyell's syndrome (toxic epidermal necrolysis), perspiration, pruritus, rash, Stevens-Johnson syndrome, urticaria, dermatitis exfoliative, and generalized bullous fixed drug eruption (GBFDE)

Renal and urinary disorders: dysuria, hematuria, renal failure including papillary necrosis and tubulointerstitial nephritis, glomerulonephritis, nephrotic syndrome

General disorders and administration site conditions: Edema

Investigations: Urobilinogen urine (false-positive), liver function test abnormal

Pediatric patients

General disorders and administration site conditions: hypothermia

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after marketing 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 requirements.

4.9. Overdose

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

For oral formulations:

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Following acute overdosage, emesis, and/or gastric lavage, and/or activated charcoal may be considered dependent upon amount ingested and time since ingestion. Vital functions should be monitored and supported. Hemodialysis is of little value since mefenamic acid and its metabolites are firmly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Mechanism of Action

Mefenamic acid is a nonsteroidal agent with demonstrated anti-inflammatory, analgesic, and antipyretic activity in laboratory animals. Mefenamic acid was found to inhibit prostaglandin synthesis and to compete for binding at the prostaglandin receptor sites in animal models.

5.2. Pharmacokinetic properties

Absorption

Mefenamic acid is rapidly absorbed from the gastrointestinal tract. Following administration of a one-gram oral dose to adults, peak plasma levels of 10 μg/mL occur in 1 to 4 hours, with a half-life of 2 hours. Plasma levels are proportional to dose, following multiple doses, with no drug accumulation. 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 extensively bound to plasma proteins.

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.

Elimination

Following a single oral dose, 52% to 67% of the dose was recovered from the urine as unchanged drug or one of two metabolites. Assay of stools over 3 days accounted for 20% to 25% of the dose, chiefly as unconjugated metabolite II.

5.3. Preclinical safety data

Rats given up to 10 times the human dose showed decreased fertility, delay in parturition, and a decreased rate of survival to weaning. No fetal abnormalities were observed in this study and in another study in dogs receiving 10 times the human dose.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Capsules

Lactose, Sodium dodecylsulfate, Dyes E132, E171, E172

Tablets

Hypromellose, macrogol 6000, magnesium stearate, methylcellulose, sodium dodecylsulfate, talc, dyes E171, E172

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Do not use PONSTAN after the expiry date which is stated on the Carton/Blister after EXP:. The expiry date refers to the last day of that month.

6.4. Special precautions for storage

Store in a cool dry place below 30ºC

6.5. Nature and contents of container

Capsules

Ponstan Capsule is available in blister packs of 250mg x 50’s

Tablets

Ponstan Tablet is available in blister pack of 500mg x 50’s

Not all strengths/pack sizes may be marketed

6.6. Special precautions for disposal and other handling

Keep out of the sight and reach of children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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

MANUFACTURED BY

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8. PRESCRIPTION STATUS

Prescription only medicine

9. DATE OF REVISION OF THE TEXT

April 2025