PT. PFIZER INDONESIA
Local Product Document

Generic Name: Mefenamic acid
Trade Name: PONSTAN
CDS Effective Date: November 01, 2019
Supersedes: November 09, 2016

Cardiovascular Risk

- 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 (see **section WARNINGS AND PRECAUTIONS**).
- PONSTAN is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **section WARNINGS AND PRECAUTIONS**).

Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (see **section WARNINGS AND PRECAUTIONS**).

DRUG PRESENTATION
Film-coated tablet.

COMPOSITION
Film-coated tablet: Mefenamic acid 500 mg.

DRUG LIST CLASSIFICATION
Prescription drug.

ACTIONS
Mefenamic acid is non-steroid anti-inflammation that act by inhibiting prostaglandin synthesis process in body tissue by inhibiting cyclo-oxygenase enzymes therefore it has analgesic, anti-inflammation, and anti-pyretic effects.

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 dose, 67% of the total dose is excreted in the urine as unchanged drug or as one of the two metabolites. 20% to 25% of the dose is excreted in the faeces during the first three days.

USAGE
Oral

INDICATIONS
Mefenamic acid is indicated for relief of mild to moderate pain in:
- Rheumatoid arthritis
- Osteoarthritis
- Muscular, traumatic, dental pain
- Headache
- Post-operative, postpartum
- Primary dysmenorrhea
- Premenstrual syndrome

CONTRAINDICATIONS
- Hypersensitivity to mefenamic acid or any components of this product.
- Patient experiencing bronchospasm, allergic rhinitis, and urticaria when treated with acetyl salicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs).
- Patient with active ulceration or chronic inflammation of either the upper or lower gastrointestinal tract.
- Patients with pre-existing renal disease.

Treatment of peri-operative pain in the setting of CABG surgery.

Patients with severe renal and hepatic failure.

Patients with severe heart failure.

DOSAGE AND 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 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.

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.

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 WARNINGS AND PRECAUTIONS – Gastrointestinal (GI) Effects**).

UNDESIRABLE EFFECTS
Blood and lymphatic system disorders: Agranulocytosis, aplastic anemia, autoimmune hemolytic anemia*, bone marrow hypoplasia, decreased hematocrit, eosinophilia, leukopenia, pancytopenia and 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 and dermatitis exfoliative.

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.

WARNINGS AND PRECAUTIONS
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 Thrombotic Events
Clinical trials of several COX-2 selective and non-selective NSAIDs of up to three years duration have shown an increase risk of serious CV thrombotic events, myocardial infarction, and stroke, which can be fatal.

All NSAIDs, both COX-2 selective and non-selective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, 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 events and the steps to take if they occur.

There is no consistent evidence that concurrent use of acetyl salicylic acid mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of acetyl salicylic acid and an NSAID does increase the risk of serious GI events (see **section WARNINGS AND PRECAUTIONS, Gastrointestinal (GI) Effect - Risk of GI Ulceration, Bleeding, and Perforation**).

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see **section CONTRAINDICATIONS**).

Hypertension

NSAIDs, including PONSTAN can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including PONSTAN, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment with PONSTAN and throughout the course of therapy.

Congestive Heart Failure and Edema
Fluid retention and edema have been observed in some patients taking NSAIDs, including PONSTAN. PONSTAN should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation
NSAIDs, including PONSTAN, can cause serious gastrointestinal events including, inflammation, bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. These trends with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in patients ingesting alcohol or patients with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids, antiplatelet drugs (such as aspirin), anticoagulants or selective serotonin reuptake inhibitors, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event, in patients treated with NSAIDs, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

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.

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.

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.

Hematologic Effects
Mefenamic acid can inhibit platelet aggregation and may prolong prothrombin time in patients on warfarin therapy (see **section DRUG INTERACTIONS)**.

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 DRUG INTERACTIONS**).

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
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. 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.

EFFECT ON ABILITY TO DRIVE AND USE MACHINES
Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

DRUG INTERACTIONS
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.

OVERDOSAGE
Following accidental overdosage, the stomach should be emptied immediately by inducing emesis or by gastric lavage, followed by administration of activated charcoal. Vital functions should be monitored and supported. Hemodialysis is of little value since mefenamic acid and its metabolites are firmly bound to plasma proteins.

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

STORAGE
Store below 30°C, protect from light.

SUPPLY
PONSTAN FCT 500 mg, box of 10 blisters @ 10 tablets; Reg. No.: DKL8519807117A1

HARUS DENGAN RESEP DOKTER

Manufactured by:
PT. Pfizer Indonesia
Jakarta, Indonesia