PRESCRIBING INFORMATION
PRODUCT MONOGRAPH

Pr PONSTAN®

Mefenamic Acid Capsules BP

250 mg

ANALGESIC

AA Pharma Inc.
1165 Creditstone Road, Unit#1,
Concord, Ontario,
L4K 4N7

Date of Preparation:
July 20, 2017

Control No. 206637

TABLE OF CONTENT

PONSTAN®
Mefenamic Acid Capsules BP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
oral	250 mg	Gelatin, Lactose, Sodium lauryl sulphate

INDICATIONS AND CLINICAL USE

Adult (>18 years old)

PONSTAN® (mefenamic acid) is indicated for the relief of pain of moderate severity in conditions such as:

- muscular aches and pains
- primary dysmenorrhea
- headache
- dental pain

For patients with an increased risk of developing CV **and/or** GI **adverse events, other management strategies that do NOT include the use of NSAIDs should be considered first. (**See **Contraindications and Warnings and Precautions)**

Use of PONSTAN® should be limited to the lowest effective dose for the shortest possible duration of treatment in order to minimize the potential risk for cardiovascular or gastrointestinal adverse events. (See **Contraindications and Warnings and Precautions)**

PONSTAN®, as a NSAID, does NOT treat clinical disease or prevent its progression.

PONSTAN®, as a NSAID, only relieves symptoms and decreases inflammation for as long as the patient continues to take it.

Patient subset

Geriatrics (>65 years old):

Evidence from clinical studies and postmarket experience suggests that use in the geriatric population is associated with differences in safety (See **Warnings and Precautions**).

Pediatrics (<18 years old):

Safety and efficacy have not been established in the pediatric population

CONTRAINDICATIONS

PONSTAN® is contraindicated in:

- the peri-operative setting of coronary artery bypass graft surgery (CABG). Although PONSTAN® has NOT been studied in this patient population, a selective COX-2 inhibitor NSAID studied in such a setting has led to an increased incidence of cardiovascular/thromboembolic events, deep surgical infections and sternal wound complications.
- the third trimester of pregnancy, because of risk of premature closure of the ductus arteriosus and prolonged parturition
- women who are breastfeeding, because of the potential for serious adverse reactions in nursing infants
- severe uncontrolled heart failure
- known hypersensitivity to PONSTAN® or to any of the components/excipients
- history of asthma, bronchospasm, urticaria, or allergic-type reactions after taking ASA or other NSAIDs (i.e. complete or partial syndrome of ASA-intolerance - rhinosinusitis, urticaria/ angioedema, nasal polyps, asthma). Fatal anaphylactoid reactions have occurred in such individuals. Individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction. The potential for cross-reactivity between different NSAIDs must be kept in mind (see **Warnings and Precautions - Hypersensitivity Reactions - Anaphylactoid Reactions**).
- active gastric / duodenal / peptic ulcer, active GI bleeding.
- cerebrovascular bleeding or other bleeding disorders
- inflammatory bowel disease
- severe liver impairment or active liver disease

- severe renal impairment (creatinine clearance <30 mL/min or 0.5 mL/sec) or deteriorating renal disease (individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored) (see **Warnings and Precautions - Renal**)
- known hyperkalemia (see **Warnings and Precautions - Renal - Fluid and Electrolyte Balance**)
- Adolescents less than 18 years of age

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Risk of Cardiovascular (CV) Adverse Events: Ischemic Heart Disease, Cerebrovascular Disease, Congestive Heart Failure (NYHA II-IV) (See Warnings and Precautions - *Cardiovascular*)

PONSTAN® is a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Caution should be exercised in prescribing PONSTAN® to any patient with ischemic heart disease (including but NOT limited to acute myocardial infarction, history of myocardial infarction and/or angina), cerebrovascular disease (including but NOT limited to stroke, cerebrovascular accident, transient ischemic attacks and/or amaurosis fugax) and/or congestive heart failure (NYHA II-IV).

Use of NSAIDs, such as PONSTAN®, can promote sodium retention in a dose-dependent manner, through a renal mechanism, which can result in increased blood pressure and/or exacerbation of congestive heart failure. (see also Warnings and Precautions - *Renal - Fluid and Electrolyte Balance*)

Randomized clinical trials with PONSTAN® have not been designed to detect differences in cardiovascular events in a chronic setting. Therefore, caution should be exercised when prescribing PONSTAN®

Risk of Gastrointestinal (GI) Adverse Events (see Warnings and Precautions* - Gastrointestinal*)

Use of NSAIDs, such as PONSTAN®, is associated with an increased incidence of gastrointestinal adverse events (such as peptic/duodenal ulceration, perforation, obstruction and gastrointestinal bleeding).

General

Frail or debilitated patients may tolerate side effects less well and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse event, the lowest effective dose should be used for the shortest possible duration**. As with other NSAIDs, caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function. For high risk patients, alternate therapies that do not involve should be considered.

PONSTAN® is NOT recommended for use with other NSAIDs , with the exception of low-dose ASA for cardiovascular prophylaxis, because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions. (See **Drug Interactions - *Drug/Drug Interactions - Acetylsalicylic acid (*ASA*)or other NSAIDS***)

If rash occurs, PONSTAN® (mefenamic acid) should be promptly discontinued.

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

The use of PONSTAN® with concomitant NSAIDs including COX-2 inhibitors should be avoided.

PONSTAN® may prolong ASA induced gastrointestinal bleeding. However, mefenamic acid itself appears to be less liable than ASA to cause gastrointestinal bleeding.

PONSTAN® 500 mg and ASA 650 mg 4 times a day both caused significant further lowering of the prothrombin concentration (mefenamic acid 3.48% and ASA 2.75%) in patients in whom the concentration had been initially lowered by anticoagulant therapy. Caution, therefore, should be exercised in administering PONSTAN® to patients on anticoagulant therapy and should not be given when prothrombin concentration is in the range of 10 to 20% normal. Careful monitoring of blood coagulation factors is recommended.

It is recommended that estimations of hemoglobin and blood counts be carried out at regular intervals.

PONSTAN® should be used with caution in known asthmatics.

Carcinogenesis and Mutagenesis

No data is available.

Cardiovascular

***PONSTAN®* is a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.**

Caution should be exercised in prescribing *PONSTAN®* to patients with risk factors for cardiovascular disease, cerebrovascular disease or renal disease, such as any of the following (NOT an exhaustive list)

- **Hypertension**
- **Dyslipidemia / Hyperlipidemia**
- **Diabetes Mellitus**
- **Congestive Heart Failure (NYHA I)**
- **Coronary Artery Disease (Atherosclerosis)**
- **Peripheral Arterial Disease**
- **Smoking**
- **Creatinine Clearance < 60 mL/min or 1 mL/sec**

Use of NSAID, such as *PONSTAN®*, can lead to new hypertension or can worsen pre-existing hypertension, either of which may increase the risk of cardiovascular events as described above. Thus blood pressure should be monitored regularly. Consideration should be given to discontinuing *PONSTAN®* should hypertension either develop or worsen with its use.

Use of NSAID, such as *PONSTAN®*, can induce fluid retention and edema, and may exacerbate congestive heart failure, through a renally-mediated mechanism. **(See Warnings and Precautions - Renal - Fluid and Electrolyte Balance).**

For patients with a high risk of developing an adverse CV event, other management strategies that do NOT include the use of should be considered first**. *To minimize the potential risk for an adverse CV event, the lowest effective dose should be used for the shortest possible duration.***

Endocrine and metabolism

Corticosteroids

PONSTAN® (mefenamic acid) is NOT a substitute for corticosteroids. It does NOT treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids. (see **Drug Interactions - Drug-Drug Interactions - *Glucocorticoids***)

Gastrointestinal (GI)

Serious GI toxicity (sometimes fatal), such as peptic / duodenal ulceration, inflammation, perforation, obstruction and gastrointestinal bleeding, can occur at any time, with or without warning symptoms, in patients treated with NSAID, such as PONSTAN®. Minor upper GI problems, such as dyspepsia, commonly occur at any time. Health care providers should remain alert for ulceration and bleeding in patients treated with PONSTAN®, even in the absence of previous GI tract symptoms. 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, the lowest effective dose should be used for the shortest possible duration**. For high risk patients, alternate therapies that do not involve should be considered. (See **Warnings and Precautions - *Special Populations - Geriatrics***)

Patients should be informed about the signs and/or symptoms of serious GI toxicity and instructed to discontinue using PONSTAN® and seek emergency medical attention if they experience any such symptoms. The utility of periodic laboratory monitoring has NOT been demonstrated, nor has it been adequately assessed. Most patients who develop a serious upper GI adverse event on NSAID therapy have no symptoms. Upper GI ulcers, gross bleeding or perforation, caused by , appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. Even short-term therapy has its risks.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g. age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

If diarrhea occurs, the dosage should be reduced or temporarily suspended (See ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION). Certain patients who develop diarrhea may be unable to tolerate the drug because of recurrence of the symptoms on subsequent exposure.

Caution should be taken if prescribing PONSTAN® to patients with a prior history of peptic / duodenal ulcer disease or gastrointestinal bleeding as these individuals have a greater than 10-fold higher risk for developing a GI bleed when taking a NSAID than patients with neither of these risk factors. Other risk factors for GI ulceration and bleeding include the following: *Helicobacter pylori* infection, increased age, prolonged use of NSAID therapy, excess alcohol intake, smoking, poor general health status or concomitant therapy with any of the following:

- Anti-coagulants (e.g. warfarin)
- Anti-platelet agents (e.g. ASA, clopidogrel)
- Oral corticosteroids (e.g. prednisone)
- Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g. citalopram, fluoxetine, paroxetine, sertraline)

Genitourinary

Some NSAIDs are associated with persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with a NSAID. Should urinary symptoms occur, in the absence of an alternate explanation, treatment with PONSTAN® should be stopped to ascertain if symptoms disappear. This should be done before urological investigations or treatments are carried out.

In chronic animal toxicity studies, PONSTAN® at 7 to 28 times the recommended human dose, caused minor microscopic renal papillary necrosis in rats, edema and blunting of the renal papilla in dogs, and renal papillary edema in monkeys. In humans, there have been reports of acute interstitial nephritis with haematuria, proteinuria and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, dysfunction, those taking diuretics and the elderly. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state. In normal human volunteers, BUN levels were slightly elevated following prolonged administration of PONSTAN® at greater than therapeutic doses. Since PONSTAN® is eliminated primarily by the kidneys, it should not be administered to patients with significantly impaired renal function.

Hematologic

NSAIDs inhibiting prostaglandin biosynthesis interfere with platelet function to varying degrees; patients who may be adversely affected by such an action, such as those on anti-coagulants or

suffering from haemophilia or platelet disorders should be carefully observed when PONSTAN® is administered.

Anti-coagulants

Numerous studies have shown that the concomitant use of NSAIDs and anti-coagulants increases the risk of bleeding. Concurrent therapy of PONSTAN® with warfarin requires close monitoring of the international normalized ratio (INR).

Even with therapeutic INR monitoring, increased bleeding may occur.

Anti-platelet Effects

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike acetylsalicylic acid (ASA), their effect on platelet function is quantitatively less, or of shorter duration, and is reversible.

PONSTAN® and other NSAIDs have no proven efficacy as anti-platelet agents and should NOT be used as a substitute for ASA or other anti-platelet agents for prophylaxis of cardiovascular thromboembolic diseases. Anti-platelet therapies (e.g. ASA) should NOT be discontinued. There is some evidence that use of NSAIDs with ASA can markedly attenuate the cardioprotective effects of ASA. (see **Drug Interactions - *Drug-Drug Interactions - Acetylsalicylic Acid (ASA) or other NSAIDs***)

Concomitant administration of PONSTAN® with low dose ASA increases the risk of GI ulceration and associated complications.

Blood dyscrasias

Blood dyscrasias (such as neutropenia, leukopenia, thrombocytopenia, aplastic anemia and agranulocytosis) associated with the use of NSAIDs are rare, but could occur with severe consequences.

Anemia is sometimes seen in patients receiving NSAIDs, including PONSTAN®. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including PONSTAN® , should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss.

Hepatic/Biliary/Pancreatic

As with other NSAIDs, borderline elevations of one or more liver enzyme tests (AST, ALT, alkaline phosphatase) may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy.

PONSTAN® should be used with caution in patients with hepatic impairment.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes, have been reported with NSAIDs.

Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop (e.g. jaundice), or if systemic manifestations occur (e.g. eosinophilia, associated with rash, etc.), this drug should be discontinued.

If there is a need to prescribe this drug in the presence of impaired liver function, it must be done under strict observation.

Hypersensitivity Reactions

Anaphylactoid Reactions

As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to PONSTAN®. In post-marketing experience, rare cases of anaphylactic/ anaphylactoid reactions and angioedema have been reported in patients receiving PONSTAN®. PONSTAN® should NOT be given to patients with the ASA-triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking ASA or other NSAIDs (see **Contraindications**).

ASA-Intolerance

PONSTAN® should NOT be given to patients with complete or partial syndrome of ASA-intolerance (rhinosinusitis, urticaria/angioedema, nasal polyps, asthma) in whom asthma, anaphylaxis, urticaria/angioedema, rhinitis or other allergic manifestations are precipitated by ASA or other NSAIDs. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction (see **Contraindications**).

Cross-sensitivity

Patients sensitive to one NSAID may be sensitive to any of the other NSAIDs as well.

Serious skin reactions

(See **Warnings and Precautions - *Skin***)

Immune

(See **Warnings and Precautions - *Infection- Aseptic Meningitis***)

Infection

PONSTAN®, in common with other NSAIDs, may mask signs and symptoms of an underlying infectious disease.

Aseptic Meningitis

Rarely, with some NSAIDs, the symptoms of aseptic meningitis (stiff neck, severe headaches, nausea and vomiting, fever or clouding of consciousness) have been observed. Patients with autoimmune disorders (systemic lupus erythematosus, mixed connective tissue diseases, etc.) seem to be predisposed. Therefore, in such patients, the health care provider must be vigilant to the development of this complication.

Neurologic

Some patients may experience drowsiness, dizziness, blurred vision, vertigo, tinnitus, hearing loss, insomnia or depression with the use of NSAIDs, such as PONSTAN®. If patients experience such adverse reaction(s), they should exercise caution in carrying out activities that require alertness.

Ophthalmologic

Blurred and/or diminished vision has been reported with the use of NSAIDs. If such symptoms develop PONSTAN® should be discontinued and an ophthalmologic examination performed. Ophthalmologic examination should be carried out at periodic intervals in any patient receiving PONSTAN® for an extended period of time.

Peri-Operative Considerations

(See **Contraindications -** Coronary Artery Bypass Graft Surgery)

Psychiatric

(See **Warnings and Precautions – *Neurologic***)

Renal

Long term administration of NSAIDs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis, hematuria, low grade proteinuria and occasionally nephrotic syndrome.

Renal insufficiency due to NSAID use is seen in patients with pre-renal conditions leading to reduction in renal blood flow or blood volume. Under these circumstances, renal prostaglandins help maintain renal perfusion and glomerular filtration rate (GFR). In these patients, administration of a NSAID may cause a reduction in prostaglandin synthesis leading to impaired renal function. Patients at greatest risk of this reaction are those with pre-existing renal insufficiency (GFR < 60 mL/min or 1 mL/s), dehydrated patients, patients on salt restricted diets, those with congestive heart failure, cirrhosis, liver dysfunction, taking angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, cyclosporin, diuretics, and those who are elderly. Serious or life-threatening renal failure has been reported in patients with normal or impaired renal function after short term therapy with NSAIDs. Even patients at risk who demonstrate the ability to tolerate a NSAID under stable conditions may decompensate during periods of added stress (e.g. dehydration due to gastroenteritis). Discontinuation of NSAIDs is usually followed by recovery to the pre-treatment state.

Caution should be used when initiating treatment with NSAIDs, such as PONSTAN®, in patients with considerable dehydration. Such patients should be rehydrated prior to initiation of therapy. Caution is also recommended in patients with pre-existing kidney disease.

Advanced Renal Disease

(See **Contraindications**)

Fluid and Electrolyte Balance*:*

Use of NSAIDs, such as PONSTAN®, can promote sodium retention in a dose-dependent manner, which can lead to fluid retention and edema, and consequences of increased blood pressure and exacerbation of congestive heart failure. Thus, caution should be exercised in prescribing PONSTAN® in patients with a history of congestive heart failure, compromised cardiac function,

hypertension, increased age or other conditions predisposing to fluid retention (See **Warnings and Precautions - *Cardiovascular***).

Use of NSAIDs, such as PONSTAN®, can increase the risk of hyperkalemia, especially in patients with diabetes mellitus, renal failure, increased age, or those receiving concomitant therapy with adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, cyclosporin, or some diuretics.

Electrolytes should be monitored periodically (see **Contraindications**).

Respiratory

ASA-induced asthma is an uncommon but very important indication of ASA and NSAID sensitivity. It occurs more frequently in patients with asthma who have nasal polyps.

Sexual Function / Reproduction

The use of PONSTAN®, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of PONSTAN® should be considered.

Skin

In rare cases, serious skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and erythema multiforme have been associated with the use of some NSAIDs. Because the rate of these reactions is low, they have usually been noted during post-marketing surveillance in patients taking other medications also associated with the potential development of these serious skin reactions. Thus, causality is NOT clear. These reactions are potentially life threatening but may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that if they experience a skin rash they should discontinue their NSAID and contact their physician for assessment and advice, including which additional therapies to discontinue.

Special Populations

Pregnant Women

PONSTAN® is CONTRAINDICATED for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and the potential to prolong parturition (see Toxicology).

Caution should be exercised in prescribing PONSTAN® during the first and second trimesters of pregnancy (see Toxicology).

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or the embryofoetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

It is not known if PONSTAN® or its metabolites crosses the placenta. Since there are no adequate and well controlled studies in pregnant women, PONSTAN® should be used only if the potential benefits to the mother justify the possible risks to the foetus.

Women on PONSTAN® therapy should consult their physician if they decide to become pregnant.

Nursing Women

Trace amounts of mefenamic acid may be present in breast milk and transmitted to the nursing infant; thus PONSTAN® should not be taken by the nursing mother because of the effects of this class of drugs on the infant cardiovascular system.
(See **Contraindications)**

Pediatrics

Safety and effectiveness in children below the age of 18 have not been established.
(See **Contraindications)**

Geriatrics

Patients older than 65 years (referred to in this document as older or elderly) and frail or debilitated patients are more susceptible to a variety of adverse reactions from NSAIDs. The incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower esophageal injury including ulceration and bleeding. For such patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision.

Monitoring and Laboratory Tests

PONSTAN® may prolong prothrombin time. Therefore when the drug is administered to patients receiving oral anticoagulant therapy, frequent monitoring of prothrombin time is necessary. The concurrent use of NSAIDs and warfarin has been associated with severe, sometimes fatal haemorrhage. Menefamic acid like other non-steroidal anti-inflammatory agents, can inhibit platelet aggregation and may prolong prothrombin time in patients on warfarin therapy. Mefenamic acid has been show to displace warfarin from protein binding sites and may enhance the response to oral anticoagulants. Concurrent administration of PONSTAN® with oral anticoagulant drugs requires frequent prothrombin time monitoring.

ADVERSE REACTIONS

Abnormal Hematologic and Clinical Chemistry Findings

Cases of autoimmune hemolytic anemia have been associated with the continuous administration of NSAIDs, including PONSTAN®, for 12 months or longer. In such cases the Coombs test results are positive, with evidence of both accelerated RBC production and RBC destruction. The process is reversible upon termination of PONSTAN® administration.

Decreases in hematocrit have been noted in 2-5% of patients and primarily in those who have received prolonged therapy.

Leukopenia, eosinophilia, thrombocytopenic purpura, agranulocytosis, pancytopenia, bone marrow hypoplasia and aplastic anemia have also been occasionally reported with NSAID treatment.

Post-market Adverse Drug Reactions

Additional reports of serious adverse events temporally associated with PONSTAN® during worldwide post-marketing experience are included below. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or clearly establish a causal relationship to PONSTAN® exposure.

Gastrointestinal: The most frequently reported adverse reactions associated with the use of PONSTAN® (mefenamic acid) involve the gastrointestinal tract. In controlled studies for up to 8 months, the following disturbances were reported in decreasing order of frequency: diarrhea (approximately 5% of patients), nausea with or without vomiting, other gastrointestinal symptoms and abdominal pain.

In certain patients, the diarrhea was of sufficient severity to require discontinuation of medication. The occurrence of diarrhea is usually dose related, generally subsides on reduction of dosage and rapidly disappears on termination of therapy.

Other gastrointestinal reactions less frequently reported were anorexia, pyrosis, flatulence, constipation, enterocolitis, colitis, steatorrhea, cholestatic jaundice, hepatitis, pancreatis, hepatorenal syndrome and mild hepatic toxicity.

Gastrointestinal ulceration with or without hemorrhage has been reported.

Nervous System: Aseptic meningitis, reversible leukoencephalopathy, dizziness, drowsiness, blurred vision, convulsions, insomnia, nervousness and headache have occurred.

Integumentary: Urticaria, rash, facial edema, angiodema, edema of the larynx, Stevens-Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis), erythema multiforme, and perspiration have been reported.

Renal: As with other NSAID agents, renal failure, including papillary necrosis, has been reported. In elderly patients, renal failure has occurred after taking PONSTAN® for 2 to 6 weeks. The renal damage may not be completely reversible. Hematuria, dysuria and hyponatremia have also been reported with PONSTAN®.

Body as a Whole: anaphylaxis.

Special Senses: eye irritation, ear pain, reversible loss of color vision.

Other: Glucose intolerance in diabetic patients, hypotension, asthma, palpitation, and dyspnea. Mild hepatic toxicity and increased need for insulin in a diabetic patient have been reported.

DRUG INTERACTIONS

Serious Drug Interactions

Corticosteroids: Concurrent use with NSAIDs may increase the risk of gastrointestinal ulceration or bleeding.

Drug-Drug Interactions

Acetylsalicylic acid (ASA) or other NSAIDs

The use of PONSTAN® in addition to any other NSAID, including over-the-counter ones (such as ASA and ibuprofen) for analgesic and/or anti-inflammatory effects is NOT recommended because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions. The exception is the use of low dose ASA for cardiovascular protection, when another

NSAID is being used for its analgesic/anti-inflammatory effect, keeping in mind that combination NSAID therapy is associated with additive adverse reactions.

The exception is the use of low dose ASA for cardiovascular protection, when another NSAID is being used for its analgesic/anti-inflammatory effect, keeping in mind that combination NSAID therapy is associated with additive adverse reactions.

Some NSAIDs (e.g. ibuprofen) may interfere with the anti-platelet effects of low dose ASA, possibly by competing with ASA for access to the active site of cyclooxygenase-1.

Anti-coagulants

The ulcerogenic potential of PONSTAN® and the effect of the drug on platelet function may further contribute to the hazard of concomitant therapy with any anticoagulant or thrombolytic agent (e.g. streptokinase).

(See **Warnings and Precautions – *Hematologic - Anti-coagulants***)

Anti-hypertensives

NSAIDs may diminish the anti-hypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors.

Combinations of ACE inhibitors, angiotensin-II antagonists, or diuretics with NSAIDs might have an increased risk for acute renal failure which is usually reversible and hyperkalemia. Blood pressure and renal function (including electrolytes) should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure.

The occurrence of these interactions should be considered in patients taking PONSTAN® with an ACE inhibitor or AIIA. 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 renal function should be assessed before, and periodically during, concomitant treatment.

Anti-platelet Agents (including ASA)

There is an increased risk of bleeding, via inhibition of platelet function, when anti-platelet agents are combined with NSAIDs, such as PONSTAN® (see **Warnings and Precautions – *Hematologic - Anti-platelet Effects***).

Cyclosporin

Concomitant administration with NSAIDs increases the risk of nephrotoxicity.

Diuretics

Clinical studies as well as post-marketing observations have shown that NSAIDs can reduce the effect of diuretics.

Glucocorticoids

Some studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI adverse events such as ulceration and bleeding. This is especially the case in older (> 65 years of age) individuals.

Lithium

Monitoring of plasma lithium concentrations is advised when stopping or starting a NSAID, as increased lithium concentrations can occur.

NSAIDS, including mefenamic acid have 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.

Oral Hypoglycemics

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 hypoglycaemic agents.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Concomitant administration of NSAIDs and SSRIs may increase the risk of gastrointestinal ulceration and bleeding (see **Warnings and Precautions - *Gastrointestinal***).

Tacrolimus

Concomitant administration with NSAIDs increases the risk of nephrotoxicity.

Protein-bound Drugs

Because PONSTAN® is highly protein bound, it could be displaced from binding sites by, or it could displace from binding sites, other protein-bound drugs such as oral anticoagulants, hydantoins, salicylates, sulphonamides and sulfonylureas. Patients receiving PONSTAN® with any of these drugs should be observed for adverse effects.

DOSAGE AND ADMINISTRATION

Adults:

Dosing Considerations

Administration is by the oral route, preferably with food.

Recommended Dose and Dosage Adjustment

Treatment of Acute Pain in Adults:

Ana

Treatment of Primary Dysmenorrhea:

PONSTAN® 250 mg capsules: 500 mg (2 capsules) as an initial dose, followed by 250 mg (1 capsule) every 6 hours.

Treatment may start with the onset of bleeding and associated symptoms. Clinical studies indicate that effective treatment can be initiated with the start of menses and should not be necessary for more than 2 to 3 days.

Missed Dose

If a dose is missed, patient should take it as soon as they remember. If it is near the time of the next dose, skip the missed dose and resume your usual dosing schedule. Do not double the dose to catch up.

Administration

Administration is by the oral route, preferably with food.

OVERDOSAGE

For management of a suspected drug overdose contact your regional Poison Control Centre

Symptoms of overdosage are related to the amount of drug ingested and range from gastrointestinal discomfort and diarrhoea to seizures, acute renal failure, coma and death. Plasma levels of up to 210 µg/mL (therapeutic range 1 to 10 µg/mL) have been reported resulting in repeated generalised convulsions, but are not generally useful for evaluation and management of overdosage.

There is no specific antidote for mefenamic acid overdose. Treatment is symptomatic and supportive, including fluid replacement and IV access especially to patients who are dehydrated or unable to ingest adequate fluids. Avoiding intravascular fluid depletion will help prevent development of renal failure.

In cases of severe toxicity, activated charcoal may reduce absorption of the drug if given within one to two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube ensuring that the airway is protected. In clinically severe overdoses, full blood count, electrolytes, glucose, renal function, liver function tests, arterial blood gases and coagulation studies should be monitored for abnormalities. Because mefenamic acid and its metabolites are firmly bound to plasma proteins, haemodialysis, haemoperfusion and peritoneal dialysis may be of little value.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

PONSTAN® (mefenamic acid), an anthranilic acid derivative, is a nonsteroidal anti-inflammatory drug (NSAID) with demonstrated anti-inflammatory, analgesic and antipyretic activity in laboratory animals. Its mode of action is not completely understood, but may be related to prostaglandin synthetase inhibition. In animal studies, the drug was found to inhibit prostaglandin synthesis and to compete for binding at the prostaglandin receptor site.

Pharmacodynamics

Mefenamic acid appears to be rapidly absorbed from the gastrointestinal tract following oral administration to humans. Peak plasma levels were reached 1 to 2 hours after administration of two 250 mg capsules; the C_{max} of free mefenamic acid was 3.5 mcg/mL and the half-life in plasma was about 3 to 4 hours. Following a single 1000 mg oral dose, peak plasma levels of 10 mcg/mL occurred in 2 to 4 hours, with a half-life of 2 hours.

Following multiple doses, plasma levels are proportional to dose with no evidence of drug accumulation. Repeated administration of PONSTAN® (250 mg capsules QID yielded peak plasma levels of 3.7 to 6.7 mcg/mL within 1 to 2.5 hours after administration of each dose.

Mefenamic acid has two distinct metabolic products, namely a hydroxymethyl and a carboxy derivative; both have been identified in both plasma and urine. The parent drug and the metabolites are conjugated with glucuronic acid and excreted primarily in the urine but to a lesser extent also in the feces. Following a single dose, 67% of the total dose is excreted in the urine as unchanged drug or as one of two metabolites. Twenty to twenty-five per cent of the dose is excreted in the feces during the first 3 days.

STORAGE AND STABILITY

Store at controlled room temperature, 15-30^{o}C. Protect from moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

PONSTAN® 250 mg, capsules

Composition

Mefenamic acid 250 mg. Nonmedicinal Ingredients: gelatin, lactose, sodium lauryl sulfate. Capsule shell ingredients: FD&C Yellow No. 6, D&C Yellow No. 10, FD&C Blue No. 1, titanium dioxide, gelatin, silicon dioxide, sodium lauryl sulfate.

A gelatin capsule no.1, opaque; the body is ivory and the cap is aqua blue, printed "250 mg" in black ink on the body.

PONSTAN® is available in bottle of 100's.

PART II: SCIENTIFIC INFORMATION

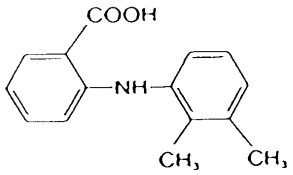
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Mefenamic Acid

Chemical Name: N-(2,3-xylyl)anthranilic acid

Structural Formula:



Molecular weight: 241.3

Description: A white to greyish-white, microcrystalline powder; odourless or almost odourless; melting point 230-231°C. Practically insoluble in water; slightly soluble in ethanol and chloroform; sparingly soluble in ether.

DETAILED PHARMACOLOGY

The analgesic and anti-inflammatory activities of PONSTAN® (mefenamic acid) have been demonstrated in laboratory animals. Using the threshold amount of pressure on the rat's tail required to elicit a squeak, mefenamic acid was 1.4 times as potent as aminopyrine as an analgesic agent.

Utilizing the ultraviolet-induced erythema method in guinea pigs, mefenamic acid was 0.5, 5 and 3.8 times as potent as phenylbutazone, ASA and aminopyrine, respectively, as an anti-inflammatory agent.

Experimental inflammatory granulation tissue growth was inhibited in both intact and adrenalectomized rats by mefenamic acid, indicating that its effects are not mediated via corticosteroids.

In contrast with hydrocortisone, which caused significant dose-related adrenal atrophy, thymus involution, and retarded growth, mefenamic acid did not exert such effects at pharmacologically active doses.

Mefenamic acid and phenylbutazone both showed a pronounced and comparable antipyretic action in rats when tested against yeast-induced fever.

Mefenamic acid did not relieve morphine abstinence signs in abstinent, morphine-habituated monkeys.

TOXICOLOGY

Acute Toxicity

Acute oral toxicity studies were carried out in mice and rats. The median lethal dose for mice and rats by the oral and parenteral route is summarized in the following table:

Summary of Oral and Parenteral Toxicity

Species	Route of Dosing	No. of Animals Per Dose	Dose Range (mg/kg)	LD_{50} (mg/kg)
Mice	Oral	5 - 20	500 - 2500	1820 $\pm$ 58
Mice	I.P.	20	125 - 625	510 $\pm$ 20
Rat	Oral	10 - 20	500 - 2500	1620 $\pm$ 65

Chronic Toxicity

Rats: In a 78-week chronic oral toxicity study three groups of 12 male and 12 female albino rats were given mefenamic acid in the diet at dose levels of approximately 23, 50, or 100 mg/kg. The fourth group served as control. In all treated groups, there was a mild depression of food intake and a moderate depression of weight gain. At doses of 50 to 100 mg/kg/day, there was evidence of intolerance.

Abnormal biochemical values, reflecting the clinical condition of moribund animals, were seen terminally.

Gross and microscopic examination revealed drug-related changes in the kidneys and small intestine. Minor papillary necrosis and epithelial cellular degeneration of the collecting tubules were found in the higher dose animals. Lesions of the small intestine, ranging from superficial mucosal erosions to massive ulceration, likewise occurred only in the higher dose groups.

Dogs: Dogs were given mefenamic acid for one year at relatively large doses ranging from 50 to 200 mg/kg/day. Vomiting and occasional diarrhea, with no clear cut evidence of a dose relationship, appeared throughout the experiment. The only significant hematologic, biochemical, or tissue evidence of intolerance was hepatocellular hydropic vacuolation in one animal and renal papillary edema in another. A dose of 400 mg/kg/day given to 2 dogs for 10 days was discontinued because of intolerance.

Monkeys: In a chronic toxicity study, monkeys tolerated the compound well at doses of 200 mg/kg/day for periods of 367 to 722 days, but at doses of 400 and 600 mg/kg/day, episodes of vomiting, convulsions and ataxia were seen in several animals. Three monkeys showed periodic transaminase value elevation. After sacrifice, microscopic lesions were detected in the kidney, heart, liver, psoas muscle, colon and stomach in animals receiving the highest dose (600 mg/kg). In the mid-dose animals (400 mg/kg), similar lesions were seen in the kidney, heart, stomach and pylorus.

Reproduction and Fertility Studies

Reproduction studies with mefenamic acid have been performed in rats, rabbits and dogs. Rats given up to 10 times the human dose showed decreased fertility, delay in parturition and a decreased rate of survival to weaning. No drug-related gross abnormalities were seen either in the mother or offspring. Rabbits at 2.5 times the human dose showed an increase in the number of resorptions. There were no fetal anomalies observed in these studies nor in dogs at up to 10 times the human dose.

REFERENCES

1. Aylward M, Maddock J, Lewis P, et al. Mefenamic acid and diclofenac sodium in osteoarthritis of the weight bearing joints: a double blind comparison. Brit J Clin Prac 1985;39:135-139.

2. Balali-Mood M, Critchley J, Proudfoot A, et al. Mefenamic acid overdosage. Lancet, June 20, 1981:1354-1356.

3. Bolcal C, Iyem H, Sargin M, Mataraci I, Yildirim V, Doganci S, Ozal E, Demirkilic U, Tatar H. Comparison of magnesium sulfate with opioid and NSAIDs on postoperative pain management after coronary artery bypass surgery. J Cardiothorac Vasc Anesth. 2005 Dec;19(6):714-8.

4. Buchanan R, et al. The breast milk excretion of mefenamic acid. Curr Ther Res 1968;10:592.

5. Buchanan RA, Eaton CJ, Koeff ST et al. The breast milk excretion of mefenamic acid. *Curr Ther Res* 1968; 10:592-596.

6. Budoff P. Use of mefenamic acid in the treatment of primary dysmenorrhea. JAMA 1979;241:2713.

7. Chan TY. Adverse interactions between warfarin and nonsteroidal antiinflammatory drugs: mechanisms, clinical significance, and avoidance. Ann Pharmacother. 1995 Dec;29(12):1274-83.

8. Corby DG, Decker WJ. Management of acute poisoning with activated charcoal. *Pediatrics* 1974; 54(3):324-328.

9. Cryer B, Feldman M. Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. Am J Med. 1998 May;104(5):413-21.

10. Delaney JA, Opatrny L, Brophy JM, Suissa S. Drug drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding. CMAJ. 2007 Aug 14;177(4):347-51.

11. Deray G, Le Hoang P, Aupetit B, Achour A, Rottembourg J, Baumelou A. Enhancement of cyclosporine A nephrotoxicity by diclofenac. Clin Nephrol. 1987 Apr;27(4):213-4.

12. Duffy CP, Elliott CJ, O'Connor RA, Heenan MM, Coyle S, Cleary IM, Kavanagh K, Verhaegen S, O'Loughlin CM, NicAmhlaoibh R, Clynes M. Enhancement of chemotherapeutic drug toxicity to human tumour cells in vitro by a subset of non-steroidal anti-inflammatory drugs (NSAIDs). Eur J Cancer. 1998 Jul;34(8):1250-9.

13. Glazko A. Experimental observations of flufenamic, mefenamic, and meclofenamic acids. Part III. Metabolic disposition of Fenamates in Medicine. A Symposium, London 1966; Annals of Physical Medicine, Supplement, pp 23-36, 1967.

14. Hall P, Maclachlan N, Thorn N, et al. Control of menorrhagia by the cyclo-oxygenase inhibitors naproxen sodium and mefenamic acid. Brit J Obstetr Gynaecol 1987;94:554-558.

15. Hebert J, Le Morvan P, Bourgouin J. Double-blind comparison of ketoprofen and mefenamic acid in the treatment of primary dysmenorrhea. Clin Therapeut 1986;8:329-335.

16. Hoppmann RA, Peden JG, and Ober SK, "Central Nervous System Side Effects of Nonsteroidal Anti-inflammatory Drugs. Aseptic Meningitis, Psychosis, and Cognitive Dysfunction," *Arch Intern Med* , 1991, 151(7):1309-13.

17. Jackson J, et al. Mefenamic acid-induced haemolytic anaemia. Brit Med J 1970;2:297.

18. MacDonald J, Neale TJ. Toxic interaction of lithium and mefenamic acid. BMJ, Nov 1988, 297(6559): 1339.

19. Macintyre I, Fink P, McGrouther R, et al. A single-blind study of naproxen sodium and mefenamic acid in minor trauma. Scot Med J 1984;29:234-237.

20. Martindale's The Extra Pharmacopoeia, 31st edition. London, 1996; pp. 58-59.

21. Miescher P. Blood dyscrasias secondary to non-steroidal anti-inflammatory drugs. Med Toxicol 1986;1:57-70.

22. Mira M, McNeil D, Fraser I, et al. Mefenamic acid in the treatment of premenstrual syndrome. Obstet Gynecol 1986;68:395-398.

23. Ostensen M. Disease specific problems related to drug therapy in pregnancy. Lupus. 2004;13(9):746-50.

24. Or S, Bozkurt A. Analgesic effect of aspirin, mefenamic acid and their combination in post-operative oral surgery pain. J Inter Med Res 1988;16:167-172.

25. Roy S. A double-blind comparison of a propionic acid derivative (ibuprofen) and a fenamate (mefenamic acid) in the treatment of dysmenorrhea. Obstet Gynecol 1983;61:628-632.

26. Sanger G, Bennett A. Fenamates may antagonize the actions of prostaglandin endoperoxides in human myometrium. Brit J Clin Pharmacol 1979;8:479.

27. Shelley RK. Lithium toxicity and mefenamic acid. A possible interaction and the role of prostoglandin inhibition. *Br J Psychiatry* Dec 1987, 151:847-8.

28. Sinniah R, Lye WC. Acute renal failure from hemoglobinuric and interstitial nephritis secondary to iodine and mefenamic acid. Clin Nephrol. 2001 Mar;55(3):254-8.

29. Skyring A, Bhanthumnavin K. Gastrointestinal bleeding: a comparison of mefenamic acid and aspirin. Med J Australia 1967;1:601.

30. Stewart I, Thomas A. Mefenamic acid compared with diclofenac sodium in elderly patients with osteoarthritis. Brit J Clin Prac 1988;42:316-320.

31. Tolman E, Partridge R. Multiple sites of interaction between prostaglandins and nonsteroidal anti-inflammatory agents. Prostaglandins 1975;9:349.

32. Turnbull A, ed. Mefenamic acid in the treatment of gynaecologic disorders. Excerpta Medica 1987;1-43.

33. White WB. Cardiovascular risk, hypertension, and NSAIDs. Curr Pain Headache Rep. 2007 Dec;11(6):428-35

34. Winder C, et al. Anti-inflammatory, antipyretic and antinociceptive properties of N-(2,3-xylyl)anthranilic acid (mefenamic acid). J Pharmacol Exp Ther 1962;138:405.

35. Yokobori S, Yokota H, Yamamoto Y. Pediatric posterior reversible leukoencephalopathy syndrome and NSAID-induced acute tubular interstitial nephritis. Pediatr Neurol. 2006 Mar;34(3):245-7.

PART III: CONSUMER INFORMATION

PONSTAN®

Mefenamic Acid Capsules BP

250 mg

Read this information each time you refill your prescription in case new information has been added. This leaflet is part III of three-part ``Product Monograph`` published when PONSTAN® was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about PONSTAN®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Your health care provider has prescribed PONSTAN® for you for one or more of the following medical conditions:

- discomfort caused by muscular aches
- headache
- primary dysmenorrhea
- dental pain.

What it does:

PONSTAN® (Mefenamic acid) as a nonsteroidal anti-inflammatory drug (NSAID), can reduce the chemicals produced by your body which cause pain and swelling. PONSTAN® has demonstrated analgesic, anti-inflammatory and antipyretic properties. These effects may be due to PONSTAN®'s dual action on prostaglandins, one of a number of hormone-like substances that participate in a wide range of body functions.
PONSTAN®, as a nonsteroidal anti inflammatory drug (NSAID), does NOT cure your illness or prevent it from getting worse. PONSTAN® can only relieve pain and reduce swelling as long as you continue to take it.

When it should not be used:

DO NOT TAKE PONSTAN® if you have any of the following medical conditions:

- **Heart bypass surgery (planning to have or recently had)**
- **Severe, uncontrolled heart failure**
- **Bleeding in the brain or other bleeding disorders**
- **Current pregnancy (after 28 weeks of pregnancy)**
- **Currently breastfeeding (or planning to breastfeed)**
- **Allergy to ASA (Acetylsalicylic Acid) or other NSAIDs (Nonsteroidal Anti-**
- **Inflammatory Drugs)**
- **Ulcer (active)**
- **Bleeding from the stomach or gut (active)**
- **Inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis)**
- **Liver disease (active or severe)**
- **Kidney disease (severe or worsening)**
- **High potassium in the blood**

Patients who took a drug in the same class as PONSTAN® after a type of heart surgery (coronary artery bypass grafting (CABG)) were more likely to have heart attacks, strokes, blood clots in the leg(s) or lung(s), and infections or other complications than those who did NOT take that drug.

PONSTAN® should NOT be used in patients under 18 years of age since the safety and effectiveness have NOT been established.

What the medicinal ingredient is:

Mefenamic Acid 250 mg

What the non medicinal ingredient are:

Gelatin, Lactose, Sodium lauryl sulphate

What dosage forms it comes in:

Each capsule contains 250 mg of Mefenamic acid

WARNING AND PRECAUTIONS

If you have, or previously had, any of the following medical conditions, see your health care provider to discuss treatment options other than PONSTAN®:

- **Heart Attack or Angina**
- **Stroke or Mini-stroke**
- **Loss of Vision**
- **Current Pregnancy (less than 28 weeks)**
- **Congestive Heart Failure**

Before taking this medication, tell your health care provider if you have any of the following:

- High blood pressure
- High cholesterol
- Diabetes mellitus or on a low sugar diet
- Atherosclerosis
- Poor circulation to your extremities
- Smoker or ex-smoker
- Kidney disease or urine problems
- Previous ulcer or bleeding from the stomach or gut
- Previous bleeding in the brain
- Bleeding problems
- Family history of allergy to NSAIDs, such as acetylsalicylic acid (ASA), celecoxib, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, rofecoxib, sulindac, tenoxicam, tiaprofenic acid, tolmetin, or valdecoxib (NOT a complete list)
- Family history of asthma, nasal polyps, long-term swelling of the sinus (chronic sinusitis) or hives
- Any other medical problem

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, if you are treated chronically with PONSTAN®.
If diarrhea or skin rash appear, you should discontinue PONSTAN® immediately.
Blood counts and liver function should be monitored during long-term therapy. PONSTAN® may enhance the effects of your oral anticoagulants medication.

Also, before taking this medication, tell your health care provider if you are planning to get pregnant.

While taking this medication:

- tell any other doctor, dentist, pharmacist or other health care professional that you see, that you are taking this medication, especially if you are planning to have heart surgery;

- do NOT drink alcoholic beverages while taking this medication because you would be more likely to develop stomach problems;

- fertility may be decreased. The use of PONSTAN® is not recommended in women trying to get pregnant. In women who have difficulty conceiving, stopping PONSTAN® should be considered.

INTERACTIONS WITH THIS MEDICATION

Talk to your health care provider and pharmacist if you are taking any other medication (prescription or non-prescription) such as any of the following (NOT a complete list):

- Acetylsalicylic Acid (ASA) or other NSAIDs
  - e.g. ASA, celecoxib, diclofenac, ibuprofen, indomethacin, ketorolac, meloxicam, naproxen
- Antacids
- Antidepressants
  - Selective Serotonin Reuptake Inhibitors (SSRIs) e.g. citalopram, fluoxetine, paroxetine, sertraline
- Blood pressure medications
- ACE (angiotensin converting enzyme) inhibitors
  - e.g. enalapril, lisinopril, perindopril, ramipril,
- ARBs (angiotensin II receptor blockers)
  - e.g. candesartan, irbesartan, losartan, valsartan
- Blood thinners
  - e.g. warfarin, ASA, clopidogrel
- Corticosteroids (including glucocorticoids)
  - e.g. prednisone
- Cyclosporin
- Digoxin
- Diuretics
  - e.g. furosemide, hydrochlorothiazide

- Lithium
- Methotrexate
- Oral contraceptives
- Oral hypoglycemics (diabetes medications)
- Tacrolimus

Your health care provider may prescribe low dose ASA (acetylsalicylic acid) as a blood thinner to reduce your risk of having a heart attack or stroke while you are taking PONSTAN®. Take only the amount of ASA prescribed by your health care provider. You are more likely to upset or damage your stomach if you take both PONSTAN® and ASA than if you took PONSTAN® alone.

PROPER USE OF THIS MEDICATION

Usual Dose

Medical Condition	Age Group	Starting Dose	Maximum Dose (per day)	Maximum Duration of Treatment (days)
Acute pain, headeach	>18 y.o	2 capsules of 250mg with meals	1250mg	7
Primary dysmenorrhea	>18 y.o	2 capsules of 250mg with meals	1250mg	3

Take PONSTAN® only as directed by your health care provider. **Do NOT take more of it, do NOT take it more often and do NOT take it for a longer period of time than your health care provider recommended. If possible, you should take the lowest dose of this medication for the shortest time period.** Taking too much PONSTAN® may increase your chances of unwanted and sometimes dangerous side effects, especially if you are elderly, have other diseases or take other medications.

If you will be using PONSTAN® for more than 7 days, see your health care provider regularly to discuss whether this medicine is working for you and if it is causing you any unwanted effects.

This medication has been prescribed specifically for you. Do NOT give it to anyone else. It may harm them, even if their symptoms seem to be similar to yours.

PONSTAN® is NOT recommended for use in patients under 18 years of age since safety and effectiveness have NOT been established.

PONSTAN® must be taken with food

Missed Dose

If a dose is missed, you should take it as soon as you remember. If it is near the time of the next dose, skip the missed dose and resume your usual dosing schedule. Do not double the dose to catch up.

Overdose

If you take more than the prescribed dose, contact your health care provider immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

PONSTAN® may cause some side effects, especially when used for a long time or in large doses. When these side effects occur, you may require medical attention. Report all symptoms or side effects to your health care provider.

PONSTAN® may cause you to become drowsy or tired. Be careful about driving or participating in activities that require you to be alert. If you become drowsy, dizzy or light-headed after taking PONSTAN®, do NOT drive or operate machinery.

Check with your health care provider IMMEDIATELY if you develop chills, fever, muscle aches or pains, or other flu like symptoms, especially if they occur before or together with a skin rash. These symptoms may be the first signs of a SERIOUS ALLERGIC REACTION to this medication.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM
All these side effects are rare.

Symptom	**STOP taking PONSTAN® and talk to your physician or pharmacist**	**STOP taking PONSTAN® and get emergency medical attention IMMEDIATELY**
Bloody or black tarry stools		✔
Shortness of breath, wheezing, any trouble breathing or chest tightness		✔
Skin rash, hives, swelling or itching		✔
Blurred vision, or any visual disturbance		✔
Any change in the amount or colour of your urine (red or brown)		✔
Any pain or difficulty experienced while urinating	✔	
Swelling of the feet, lower legs; weight gain	✔	
Vomiting or persistent indigestion, nausea, stomach pain or diarrhea	✔	
Yellow discolouration of the skin or eyes, with or without itchy skin	✔ Call your doctor immediately	
Malaise, fatigue, loss of appetite	✔	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM All these side effects are rare.		
Symptom	**STOP taking PONSTAN® and talk to your physician or pharmacist**	**STOP taking PONSTAN® and get emergency medical attention IMMEDIATELY**
Headaches, stiff neck	✔	
Mental confusion, depression	✔	
Dizziness, lightheadedness	✔	
Hearing problems	✔	

This is NOT a complete list of side effects. If you develop any other symptoms while taking PONSTAN®, see your health care provider. These side effects are rare.

HOW TO STORE IT

Do NOT keep outdated medicine or medicine no longer needed. Any outdated or unused medicine should be returned to your pharmacist.

Keep the capsules in a dry place at normal room temperature (15°C- 30°C) in the packaging that they come in.

Keep out of reach of children.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9
    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, AA Pharma Inc. at:

1-877-998-9097

This leaflet was prepared by AA Pharma Inc.

Last revised: July 20, 2017