PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

^{Pr}PONSTAN®

Mefenamic Acid Capsules

Capsules, 250 mg, for oral use

BP

Non-Steroidal Anti-Inflammatory Drug (NSAID)

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RECENT MAJOR LABEL CHANGES

3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risk in Pregnancy	04/2024
7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests	04/2024
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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Cardiovascular, and 7 WARNINGS AND PRECAUTIONS, Gastrointestinal).

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 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Cardiovascular, and 7 WARNINGS AND PRECAUTIONS, Gastrointestinal).

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.

1.1 Pediatrics

Pediatrics (<18 years of age): PONSTAN is contraindicated in the pediatric population (see 2 CONTRAINDICATIONS and 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (>65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

PONSTAN is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- 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.
- During the third trimester of pregnancy, because of risk of premature closure of the ductus arteriosus and prolonged parturition (see 7.1.1 Pregnant Women).
- Women who are breastfeeding, because of the potential for serious adverse reactions in breastfeeding infants (see 7.1.2 Breastfeeding).
- Severe uncontrolled heart failure (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).
- 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 7 WARNINGS AND PRECAUTIONS, Immune, Anaphylactoid Reactions).
- Active gastric / duodenal / peptic ulcer, active GI bleeding (see 7 WARNINGS AND PRECAUTIONS, Gastrointestinal).
- Cerebrovascular bleeding or other bleeding disorders.
- Inflammatory bowel disease.
- Severe liver impairment or active liver disease (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).
- 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 7 WARNINGS AND PRECAUTIONS, Renal).
- Known hyperkalemia (see 7 WARNINGS AND PRECAUTIONS, Renal, Fluid and Electrolyte Balance).
- Children and adolescents less than 18 years of age.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Risk of Cardiovascular (CV) Adverse Events: Ischemic Heart Disease, Cerebrovascular Disease, Congestive Heart Failure (NYHA II-IV)** (see 7 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 7 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 7 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).

- **Risk in Pregnancy**

  Caution should be exercised in prescribing PONSTAN during the first and second trimesters of pregnancy. Use of NSAIDS at approximately 20 weeks of gestation or later may cause fetal renal dysfunction leading to oligohydramnios and neonatal renal impairment or failure (see 7.1.1 Pregnant Women). PONSTAN is contraindicated for use during the third trimester because of risk of premature closure of the ductus arteriosus and uterine inertia (prolonged parturition) (see 2 CONTRAINDICATIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Use of PONSTAN should be limited to the lowest effective dose for the shortest possible duration of treatment (see 1 INDICATIONS).

- PONSTAN is NOT recommended for use with other NSAIDs, including COX-2 inhibitors, 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 9.4 Drug-Drug Interactions, Acetylsalicylic acid (ASA)or other NSAIDS).
- For geriatric patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, 7 WARNINGS AND PRECAUTIONS, Gastrointestinal and 7 WARNINGS AND PRECAUTIONS, Renal).

4.2 Recommended Dose and Dosage Adjustment

Treatment of Acute Pain in Adults:

PONSTAN 250 mg capsules: 500 mg (2 capsules) as an initial dose, followed by 250 mg (1 capsule) every 6 hours as needed. Treatment usually should not exceed one week.

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.

Pediatrics (< 18 years of age): PONSTAN is contraindicated for use in pediatric patients (see 2 CONTRAINDICATIONS and 7.1.3 Pediatrics).

4.4 Administration

Administration is by the oral route, preferably with food.

4.5 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, the missed dose should be skipped and the usual dosing schedule should be resumed. The dose should not be doubled to catch up.

5 OVERDOSAGE

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 mcg/mL (therapeutic range 1 to 10 mcg/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, hemodialysis, hemoperfusion and peritoneal dialysis may be of little value.

For management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Capsule, 250 mg of mefenamic acid	D&C Yellow No. 10, FD&C Blue No. 1, FD&C Yellow No. 6, gelatin, lactose, silicon dioxide, sodium lauryl sulfate, titanium dioxide.

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.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

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 7 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 NSAIDs 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 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 9.4 Drug-Drug Interactions, Glucocorticoids).

Gastrointestinal

Serious gastrointestinal (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. Healthcare professionals 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 7.1.4 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 NSAIDs, appear to occur in approximately 1% of patients treated for 3 to 6 months, and in about 2 to 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 8 ADVERSE REACTIONS and 4 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.

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 (see 9.4 Drug-Drug Interactions, Anticoagulants).

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.

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 9.4 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.

Immune

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 2 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 2 CONTRAINDICATIONS).

Cross-sensitivity: Patients sensitive to one NSAID may be sensitive to any of the other NSAIDs as well.

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 pre-disposed. Therefore, in such patients, the healthcare professional must be vigilant to the development of this complication.

Monitoring and Laboratory Tests

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.

Hematology: 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. Mefenamic 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.

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

Pregnancy: If PONSTAN is administered in the middle (approximately 20 weeks) to the end of the second trimester, it is recommended that pregnant women on PONSTAN be closely monitored for amniotic fluid volume since PONSTAN may result in reduction of amniotic fluid volume and even oligohydramnios (see 7.1.1 Pregnant Women). PONSTAN is contraindicated for use in the third trimester of pregnancy.

Neurologic

Some patients may experience drowsiness, dizziness, blurred vision, vertigo, tinnitus, hearing loss, 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 2 CONTRAINDICATIONS, Coronary Artery Bypass Graft Surgery.

Psychiatric

Some patients may experience insomnia or depression with the use of NSAIDs, such as PONSTAN (see 7 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.

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 (see 16 NON-CLINICAL TOXICOLOGY). 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.

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 2 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 7 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 2 CONTRAINDICATIONS).

Reproductive Health: Female and Male Potential

- **Fertility**

  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.

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.

PONSTAN should be used with caution in known asthmatics.

Skin

Serious skin reactions: Use of some NSAIDs, such as PONSTAN, have been associated with rare post-market cases of serious, fatal or otherwise life-threatening skin reactions, including:

- drug reaction with eosinophilia and systemic symptoms (DRESS)
- Stevens-Johnson syndrome,
- toxic epidermal necrolysis,
- exfoliative dermatitis and
- erythema multiforme.

Patients appear to be at higher risk for these events early in the course of therapy, with the onset of cases usually occurring within the first month of treatment. These reactions may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that they should discontinue their NSAID at the first appearance of a skin rash, mucosal lesions or any other sign of hypersensitivity, and contact their physician immediately for assessment and advice, including which therapies to discontinue.

DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection, and eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident.

7.1 Special Populations

7.1.1 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 2 CONTRAINDICATIONS and 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology). Caution is recommended in prescribing PONSTAN during the first and second trimesters of pregnancy, particularly from the middle to end of the second trimester of pregnancy (onset at approximately 20 weeks) due to possible fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment or failure. (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

Published studies and post-marketing reports describe maternal NSAID use at approximately 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to

oligohydramnios, and in some cases, neonatal renal impairment or failure. NSAIDs were shown to cause significant reduction in fetal urine production prior to reduction of amniotic fluid volume. There have also been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction and renal impairment without oligohydramnios, some of which were irreversible, even after treatment discontinuation.

These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Complications of prolonged oligohydramnios may for example, include limb contractures and delayed lung maturation. In some post-marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If after careful consideration of the benefit-risk, NSAID treatment is considered necessary to be administered anywhere from the middle (onset at approximately 20 weeks) to the end of the second trimester of pregnancy, the use should be limited to the lowest effective dose and shortest duration possible. It is also recommended that ultrasound monitoring of amniotic fluid be considered if PONSTAN treatment extends beyond 48 hours and that NSAIDs treatment be discontinued if oligohydramnios occurs, followed by appropriate medical follow up.

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or 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.

7.1.2 Breastfeeding

Trace amounts of mefenamic acid may be present in breast milk and transmitted to the breastfeeding infant; thus PONSTAN should not be taken by the breastfeeding mother because of the effects of this class of drugs on the infant cardiovascular system (see 2 CONTRAINDICATIONS).

7.1.3 Pediatrics

Pediatrics (<18 years of age): PONSTAN is contraindicated for use in pediatric patients (see 2 CONTRAINDICATIONS).

7.1.4 Geriatrics

Geriatrics (>65 years of age): 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. To minimize the potential risk for an adverse event, the lowest effective dose should be used for the shortest possible duration. 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. For high risk patients, alternate therapies that do not involve PONSTAN should be considered (see 4.1 DOSAGE AND ADMINISTRATION, Dosing Considerations, 7 WARNINGS AND PRECAUTIONS, Cardiovascular, 7 WARNINGS AND PRECAUTIONS, Gastrointestinal and 7 WARNINGS AND PRECAUTIONS, Renal).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse reactions encountered with nonsteroidal anti-inflammatory drugs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred, particularly in the elderly. Gastrointestinal adverse events can develop at any time in the course of the therapy. (See 7 WARNINGS AND PRECAUTIONS, Gastrointestinal).

In patients taking mefenamic acid or other NSAIDs, the most frequently reported adverse experiences occurring in approximately 1 to 10% of patients are:

Gastrointestinal experiences including - abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, GI ulcers (gastric/duodenal), vomiting, abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes, tinnitus

8.2 Clinical Trial Adverse Reactions

No data are available at the time of authorization.

8.3 Less Common Clinical Trial Adverse Reactions

No data are available at the time of authorization.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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 to 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.

8.5 Post-market Adverse 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.

Body as a whole: fever, infection, sepsis, asthenia, malaise, death.

Cardiac disorders: Palpitation, arrhythmia, myocardial infarction, palpitations, congestive heart failure, tachycardia, syncope.

Ear and labyrinth disorders: Ear pain, hearing impairment.

Eye disorders: Blurred vision, eye irritation, conjunctivitis, reversible loss of color vision.

Gastrointestinal disorders: The most frequently reported adverse reactions associated with the use of PONSTAN 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 pyrosis, flatulence, constipation, enterocolitis, colitis, steatorrhea, pancreatitis.

Gastrointestinal ulceration with or without hemorrhage, rectal bleeding, pancreatitis, melena, dry mouth, stomatitis, eructation, esophagitis, gastritis, glossitis, hematemesis have been reported.

Hematologic: eosinophilia, leukopenia, thrombocytopenia, agranulocytosis, pancytopenia, hemolytic anemia, aplastic anemia.

Hepatobiliary disorders: Cholestatic jaundice, hepatitis, liver failure, hepatorenal syndrome and mild hepatic toxicity have been reported less frequently.

Immune system disorders: Facial edema, angioedema, edema of the larynx, anaphylaxis and anaphylactoid reactions have been reported.

Lymphatic system: lymphadenopathy.

Metabolism and nutrition disorders: Anorexia, weight changes, appetite changes, hyperglycemia, glucose intolerance in diabetic patients has been reported.

Mild hepatic toxicity and increased need for insulin in a diabetic patient have been reported.

Nervous system disorders: Aseptic meningitis, coma, hallucinations, reversible leukoencephalopathy, dizziness, drowsiness, vertigo, convulsions, tremors, paresthesia, and headache have occurred.

Psychiatric disorders: Insomnia, somnolence, anxiety, nervousness, confusion, depression, dream abnormalities, have occurred.

Renal and urinary disorders: 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, cystitis, interstitial nephritis, oliguria/polyuria, proteinuria and hyponatremia have also been reported with PONSTAN.

Respiratory, thoracic and mediastinal disorders: Asthma, dyspnea, respiratory depression, pneumonia.

Skin and subcutaneous tissue disorders: Urticaria, rash, angioedema, Stevens-Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis), erythema multiforme, exfoliative dermatitis, alopecia, photosensitivity, pruritus, ecchymosis, purpura, and perspiration have been reported.

Vascular disorders: Hypotension, hypertension, vasculitis.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

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

9.2 Drug Interactions Overview

Mefenamic acid is highly protein bound in plasma. It is metabolised by CYP2C9, and its metabolites, as well as mefenamic acid directly, can be glucuronidated. A number of compounds are inhibitors of CYP2C9. Drug interactions studies of mefenamic acid and these compounds have not been conducted. The possibility of altered safety and efficacy should be considered when PONSTAN is used concomitantly with these drugs.

9.3 Drug-Behaviour Interactions

Alcoholic beverages while taking PONSTAN make it more likely to develop gastrointestinal problems.

PONSTAN is contraindicated in heavy drinkers (see 2 CONRAINDICATIONS).

9.4 Drug-Drug Interactions

The drugs listed in Table 2 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 2 - Established or Potential Drug-Drug Interactions

Proper / Common name	Source of Evidence	Effect	Clinical comment
Acetylsalicylic acid (ASA) or other NSAIDs	CT	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.	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.
Anti-coagulants	CT	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).	Anticoagulation/INR should be monitored (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Anti-coagulants).

Proper / Common name	Source of Evidence	Effect	Clinical comment
Anti-hypertensives	T	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	The concomitant administration of anti-hypertensive 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 (see 7 WARNINGS AND PRECAUTIONS, Renal, Fluid and Electrolyte Balance).
Anti-platelet Agents (including ASA)	CT	There is an increased risk of bleeding, via inhibition of platelet function, when anti-platelet agents are combined with NSAIDs, such as PONSTAN.	Monitor patients for signs of bleeding (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Anti-platelet Effects).
Cyclosporin	T	Concomitant administration with NSAIDs increases the risk of nephrotoxicity.	Patients should be monitored for necessary dosage adjustment. Monitor patients for signs of worsening renal function.
Diuretics	T	Clinical studies as well as post-marketing observations have shown that NSAIDs can reduce	Observe patients for signs of worsening renal function, in addition to

Proper / Common name	Source of Evidence	Effect	Clinical comment
		the effect of diuretics.	assuring diuretic efficacy including antihypertensive effects (see 7 WARNINGS AND PRECAUTIONS, Renal).
Glucocorticoids	CT	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.	Monitor patients particularly those over 65 years of age for signs of bleeding (see 7 WARNINGS AND PRECAUTIONS, Gastrointestinal).
Lithium	CT	NSAIDS, including mefenamic acid have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance.	When PONSTAN and lithium are administered concurrently, patients should be observed carefully for signs of lithium toxicity. Monitoring of plasma lithium concentrations is advised when stopping or starting a NSAID, as increased lithium concentrations can occur.
Methotrexate	T	NSAID administration may result in increased plasma levels of methotrexate.	Caution is advised when methotrexate is administered concurrently with NSAIDs, including mefenamic acid.
Oral Hypoglycemics	T	There have been reports of changes in the effects of oral hypoglycemic agents in the presence of NSAIDs.	Mefenamic acid should be administered with caution in patients receiving insulin or oral hypoglycemic agents.
Protein-bound Drugs	CT	Because PONSTAN is highly protein bound, it could be displaced from binding sites	Patients receiving PONSTAN with any of the protein-bound drugs

Proper / Common name	Source of Evidence	Effect	Clinical comment
		by, or it could displace from binding sites, other protein-bound drugs such as oral anticoagulants, hydantoins, salicylates, sulphonamides and sulfonylureas.	should be observed for adverse effects.
Selective Serotonin Reuptake Inhibitors (SSRIs)	C	Concomitant administration of NSAIDs and SSRIs may increase the risk of gastrointestinal ulceration and bleeding.	Monitor patients for signs of bleeding (see 7 WARNINGS AND PRECAUTIONS, Gastrointestinal).
Tacrolimus	C	Concomitant administration with NSAIDs increases the risk of nephrotoxicity.	Monitor patients for signs of nephrotoxicity (see 7 WARNINGS AND PRECAUTIONS, Renal)

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

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.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 Pharmacodynamics

The analgesic and anti-inflammatory activities of PONSTAN 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.

10.3 Pharmacokinetics

Absorption

Mefenamic acid appears to be rapidly absorbed from the gastrointestinal tract following oral administration to humans.

Distribution

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 four times a day (q.i.d) yielded peak plasma levels of 3.7 to 6.7 mcg/mL within 1 to 2.5 hours after administration of each dose.

Metabolism

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.

Elimination

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.

Special Populations and Conditions

- **Pediatrics:** The safety and efficacy of mefenamic acid in pediatric patients has not been established. See 2 CONTRAINDICATIONS.
- **Geriatrics:** See 7.1.4 Geriatrics.
- **Sex:** This information is not available for this drug product.
- **Pregnancy and Breastfeeding:** See 7.1.1 Pregnant Women and 7.1.2 Breastfeeding.
- **Genetic Polymorphism:** This information is not available for this drug product.
- **Ethnic Origin:** This information is not available for this drug product.
- **Hepatic Insufficiency:** See 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic.
- **Renal Insufficiency:** See 7 WARNINGS AND PRECAUTIONS, Renal.
- **Obesity:** This information is not available for this drug product.

11 STORAGE, STABILITY AND DISPOSAL

Store at controlled room temperature, 15°C to 30°C. Protect from moisture.

12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

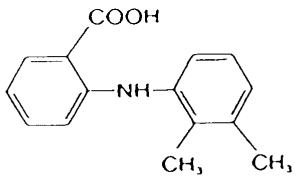
Drug Substance

Proper Name: Mefenamic Acid

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

Molecular formula and molecular mass $C_{15}H_{15}NO_2$, 241.3 g/mol

Structural Formula:



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

14 CLINICAL TRIALS

No information available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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:

Table 3 - 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 ± 58
Mice	I.P.	20	125 - 625	510 ± 20
Rat	Oral	10 - 20	500 - 2500	1620 ± 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.

Reproductive and Developmental Toxicology

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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrPONSTAN®

Mefenamic Acid Capsules

Read this carefully before you start taking **PONSTAN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **PONSTAN**.

Serious Warnings and Precautions

Heart and blood vessel problems:

- PONSTAN can cause heart and blood vessel problems like heart attacks, stroke, blood clots, high blood pressure and heart failure. These can lead to death.
- The risk of having heart problems is higher if you take PONSTAN for long periods of time and/or at higher doses and/or in people who have heart disease.
- Tell your healthcare professional if you have or have had heart problems, high blood pressure or diabetes.

Stomach and intestine (gastrointestinal) problems:

- PONSTAN can cause stomach and intestine problems like ulcers, inflammation, bleeding, holes/perforation, blockage or pain.

Pregnancy:

- **DO NOT** take PONSTAN if you are pregnant and in a later stage of pregnancy (28 weeks or later).
- If you are pregnant and in an earlier stage of pregnancy (less than 28 weeks) **only** take PONSTAN if you are told to do so by your healthcare professional.
- Medicines like PONSTAN may cause harm to you and your baby. Your healthcare professional will need to closely monitor your health and that of your baby (including your amniotic fluid levels) if they prescribe PONSTAN during this time.
- Tell your healthcare professional right away if you become pregnant, think you may be pregnant or want to get pregnant during your treatment with PONSTAN.

What is PONSTAN used for?

PONSTAN is used in adults to treat:

- discomfort caused by muscular aches
- headache
- period cramps (primary dysmenorrhea)

- dental pain

How does PONSTAN work?

PONSTAN belongs to a group of medicines called nonsteroidal anti-inflammatory drugs (NSAIDs). It works by reducing the chemicals produced by your body which cause pain and swelling.

PONSTAN only relieves pain and reduces swelling as long as you continue to take it. It does NOT cure your illness or stop it from getting worse.

What are the ingredients in PONSTAN?

Medicinal ingredients: Mefenamic Acid

Non-medicinal ingredients: D&C Yellow No. 10, FD&C Blue No. 1, FD&C Yellow No. 6, gelatin, lactose, silicon dioxide, sodium lauryl sulfate, titanium dioxide.

PONSTAN comes in the following dosage forms:

Capsules: 250 mg

Do not use PONSTAN if:

- you are allergic to mefenamic acid or any of the other ingredients in this medicine.
- you have developed asthma, hives, growths in your nose, sinus swelling or symptoms of an allergic reaction after taking acetylsalicylic acid (ASA) or other NSAIDs.
- you have recently had or are planning to have heart bypass surgery.
- you have severe, uncontrolled heart failure.
- you have bleeding in the brain or have other bleeding disorders.
- you are pregnant and in a later stage of pregnancy (28 weeks or later).
- you are currently breastfeeding (or planning to breastfeed).
- you have active stomach or intestinal ulcers.
- you have active bleeding from the stomach or gut.
- you have inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis).
- you have liver disease (active or severe).
- you have kidney disease (severe or worsening).
- you have high potassium in the blood.
- you are under 18 years old.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PONSTAN. Talk about any health conditions or problems you may have, including if you:

- have a condition that makes you frail or weak.
- have or have had a heart attack, chest pain, heart disease, stroke or heart failure.
- have high blood pressure, high cholesterol, diabetes or are on a low sugar diet.

- have a condition called atherosclerosis, this is when fats and cholesterol build up in your arteries.
- have poor blood flow to your extremities (like your hands and feet).
- smoke or used to smoke.
- have liver or kidney problems, urine problems or are dehydrated.
- are on a low-salt diet.
- have history of ulcer or bleeding from the stomach or gut (small or large intestines).
- drink a lot of alcohol.
- have history of bleeding in the brain.
- have bleeding or blood problems.
- have immune system problems.
- have asthma.
- are older then 65 yeas of age.
- are pregnant, planning on becoming or become pregnant while taking PONSTAN.
- have had difficulty conceiving in the past.
- are taking any other NSAID medicines including acetylsalicylic acid (ASA).
- are lactose intolerant or have one of the following rare hereditary diseases, because PONSTAN contains lactose:
    - Galactose intolerance
    - Lapp lactase deficiency
    - Glucose-galactose malabsorption

Other warnings you should know about:

Serious Side Effects: PONSTAN can cause serious side effects, including:

- **Blood and Bleeding Problems:** PONSTAN can cause blood problems, bleeding and prolonged bleeding. Taking PONSTAN with the following medicines can increase the risk of bleeding:
    - anticoagulants (prevent blood clots), corticosteroids (anti-inflammatory) or antidepressants like selective serotonin reuptake inhibitors (SSRIs).
- **Serious Skin Reactions:** In rare cases, serious or life-threatening skin reactions listed below have been reported with some NSAIDs, such as PONSTAN.
    - Drug reaction with eosinophilia and systemic symptoms (DRESS)
    - Stevens-Johnson syndrome (SJS),
    - toxic epidermal necrolysis (TEN),
    - exfoliative dermatitis and
    - erythema multiforme

    You may be at a greater risk of experiencing a serious skin reaction usually during the first month of treatment. See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

Check-Ups and Testing: You will have regular visits with your healthcare professional during your treatment with PONSTAN to monitor your health. They will:

- check your blood pressure.
- check your eyes. PONSTAN can cause blurred or reduced vision.
- do blood and urine tests to check your liver, kidney and blood health.

Surgery: Tell any doctor, dentist, pharmacist or healthcare professional that you see that you are taking this medicine. This is especially important if you are planning to have heart surgery.

Driving and Using Machines: PONSTAN may cause blurred vision, hearing problems, drowsiness, or dizziness. 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.

Fertility in Women: PONSTAN may affect your fertility. This means that it may be difficult for you to have a child. If you have trouble having a child, you might need to stop taking PONSTAN. Talk to your healthcare professional if you have questions about this.

Adults (65 years or older): Side effects like gastrointestinal problems may happen more often. Your healthcare professional might have you start with a lower dose of PONSTAN. They will monitor your health during and after treatment.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions
Corticosteroids: Use of corticosteroids with NSAIDs may increase your risk of gastrointestinal ulceration or bleeding.

The following may also interact with PONSTAN:

- Alcohol.
- Acetylsalicylic Acid (ASA) or other NSAIDs, used to treat pain, fever and inflammation like celecoxib, diclofenac, ibuprofen, naproxen.
- Medicines used as blood thinners to prevent blood clots like warfarin, ASA, clopidogrel.
- Medicines used to treat high blood pressure like enalapril, ramipril, candesartan, irbesartan, propranolol, atenolol.
- Medicines used to lower the risk of organ rejection like cyclosporine, tacrolimus.
- Medicines used to lower extra fluid levels (diuretics), like furosemide.
- Medicines used to treat depression (antidepressants) like citalopram, fluoxetine, paroxetine, and sertraline.
- Lithium, used to treat mania that is part of bipolar disorder (manic-depressive illness).
- Medicines used to treat different cancers, like methotrexate.
- Medicines used to treat diabetes, like sulphonyl urea or other oral hypoglycemics like glibenclamide, metformin, chlorpropamide or phenformin, tolbutamide.
- Medicines used to treat bacterial infections (antibiotics), like sulphonamide.
- Medicines used to treat seizures like phenytoin, hydantoin.

How to take PONSTAN:

- Take PONSTAN only as directed by your healthcare professional. 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 healthcare professional recommended. 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.
- Take PONSTAN by mouth, preferably with food.
- If you will be using PONSTAN for more than 7 days, see your healthcare professional regularly to discuss whether this medicine is working for you and if it is causing any side 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.

Usual dose:

Adults 18 years and older:

Your healthcare professional will decide on the best dosage for you based on your condition. They may lower your dose, stop your treatment for a period of time or recommend that you stop treatment completely. This may happen if you experience serious side effects, or if your disease gets worse.

For acute pain and headache:

- The usual dose is 2 capsules (500 mg) with meals, followed by 1 capsule (250 mg) every 6 hours as needed.
- The maximum dose is 5 capsules (1250 mg) per day.
- Maximum duration of treatment: **7 days**.

For relief of cramping pain that comes before or during a period:

- The usual dose is 2 capsules (500 mg) with meals, followed by 1 capsule (250 mg) every 6 hours.
- The maximum dose is 5 capsules (1250 mg) per day.
- Maximum duration of treatment: **3 days**.

Overdose:

If you think you, or a person you are caring for, have taken too much PONSTAN, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If a dose is missed, 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.

What are possible side effects from using PONSTAN?

These are not all the possible side effects you may have when taking PONSTAN. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Nausea, vomiting, diarrhea, constipation, stomach upset/abdominal pain, heartburn, indigestion, feeling gassy
- Headache, dizziness, drowsiness, light-headedness
- Loss of appetite
- Confusion, hard to concentrate or think, short-term memory loss
- Nervousness, trouble sleeping
- Bruises
- Sweating
- Skin rash
- Thirst, dry mouth
- Mouth sores
- Hair loss

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Cystitis (bladder infection): increased need to urinate, pain in the pelvis or lower back, frequent urination during the night, cloudy urine that may contain blood, burning or pain urinating		✓	
Gastrointestinal (GI) problems (bleeding, blockage, holes, ulcers or inflammation in your GI tract): blood in vomit, black tarry or bloody stool, dizziness, stomach pain, bloating, loss of appetite, weight loss, nausea, vomiting, constipation or diarrhea, chills or fever		✓	
Tinnitus (hearing problems): ringing, buzzing, clicking or hissing in the ears, loss of hearing		✓	
UNCOMMON			

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Anaphylaxis/hypersensitivity (severe allergic reaction): sudden wheeziness and chest pain or tightness, swelling of the eyelids, face, lips, tongue or throat, swelling or anaphylactic reaction/shock			✓
Aseptic meningitis (inflammation of the protective lining of the brain that is not caused by infection): headaches, stiff neck, nausea, vomiting, fever or clouding of consciousness		✓	
Blood problems (low white and/or red blood cell or platelet count): feeling tired or weak, pale skin, bruising or bleeding for longer than usual after you hurt yourself, fever, chills		✓	
Congestive heart failure (heart does not pump blood as well as it should): shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise			✓
Depression (sad mood that will not go away): difficulty sleeping or sleeping too much, changes in appetite or weight, reduced sex drive and thoughts of death or suicide		✓	
Eye problems: blurred vision, loss of vision in eye, increased sensitivity of the eyes to light, eye pain or redness		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Hypertension (high blood pressure): fatigue, dizziness or fainting, chest pain	✓		
Kidney disorder/problems (including kidney failure): nausea, vomiting, fever, swelling of extremities, fatigue, thirst, dry skin, irritability, dark urine, increased or decreased urine output, blood in the urine, rash, weight gain (from retaining fluid), loss of appetite, mental status changes (drowsiness, confusion, coma)		✓	
Liver problems (including hepatitis, liver failure, cholestasis): yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, unusual tiredness		✓	
Lung problems, asthma: increased shortness of breath, wheezing, difficulty breathing, cough and chest tight ness, irregular heartbeat			✓
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Stroke (bleeding or blood clot in the brain): sudden numbness, weakness or tingling of the face, arm, or leg, particularly on one side of the body, sudden headache, blurry vision, difficulty swallowing or speaking, lethargy, dizziness, fainting, vomiting, trouble understanding, trouble with walking and loss of balance			✓
Vertigo (a sense of severe spinning, dizziness, light-headedness)		✓	
RARE			
Serious Skin Reactions: fever, severe rash, swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, swelling of face and/or legs, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine or dark urine			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

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

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

Keep out of reach and sight of children.

If you want more information about PONSTAN:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://www.aapharma.ca/en/), or by calling 1-877-998-9097.

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