

## DATA SHEET

# PONSTAN<sup>®</sup>

---

### Name of Medicine

---

PONSTAN capsules contain the active ingredient mefenamic acid 250 mg/capsule.

Mefenamic acid is one of the fenamate series of nonsteroidal anti-inflammatory agents. The drug is almost insoluble in water but soluble in alkali hydroxides and alcohol.

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

Molecular formula: C<sub>15</sub>H<sub>15</sub>NO<sub>2</sub>

Molecular weight: 241.3

---

### Presentation

---

PONSTAN capsules have an opaque aqua blue cap and opaque ivory body with “PARKE DAVIS” printed in black on both the body and cap.

---

### Uses

---

#### Pharmacology

PONSTAN has demonstrated analgesic, anti-inflammatory and antipyretic properties in human clinical studies and in classical animal test systems. These effects may be due to PONSTAN's dual action on prostaglandins. It inhibits the enzymes of prostaglandin synthetase and also antagonises the actions of prostaglandin at the receptor sites. These effects may also be responsible for its effectiveness in the treatment of primary dysmenorrhoea. The pain of primary dysmenorrhoea is thought to be due to increased abnormal uterine activity and uterine ischaemia, probably induced by release of PGF<sub>2α</sub> or due to increase in the ratio of PGF<sub>2α</sub>: PGE<sub>2</sub>. Prostaglandins are also believed to be responsible, at least in some part, for the symptoms of menorrhagia. The dual mode of action of PONSTAN offers significant advantages in certain gynaecological indications over other non-steroidal anti-inflammatory agents which merely inhibit prostaglandin synthesis.

#### Pharmacokinetics

Single and multiple studies have shown that PONSTAN usually reaches peak plasma levels 2 to 4 hours after oral administration with a half life of 2 hours.

Mefenamic acid and its metabolites are firmly bound to plasma proteins.

Mefenamic acid metabolism is predominantly mediated via cytochrome P450 CYP 2C9 in the liver. Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates, should be administered

mefenamic acid with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Two distinct metabolic products, one a hydroxymethyl derivative and the other a carboxy derivative, have been identified in both plasma and urine. Mefenamic acid and its two metabolic derivatives become conjugated with glucuronic acid through an ester linkage which is alkali labile and are excreted principally in the urine, but also to some extent in the bile and faeces.

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

## **Indications**

PONSTAN is indicated for the treatment of primary dysmenorrhoea, dysfunctional uterine bleeding and pain or menorrhagia due to IUCDs.

It is also effective in pain of miscellaneous origin, including arthritic, soft tissue and dental pain.

PONSTAN has demonstrated antipyretic action in certain febrile conditions.

---

## **Dosage and Administration**

---

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

### **Dysmenorrhoea**

2 capsules (500 mg) three times daily with meals from the onset of pain and continued for the usual duration of pain.

### **Menorrhagia**

2 capsules (500 mg) three times daily with meals and from the onset of menses and continued according to the judgement of the physician. Therapy should not be continued for more than 7 days except on the advice of a physician.

### **Other Indications**

2 capsules (500 mg) three times daily, with meals.

### **Elderly and Renal Dysfunction**

Caution is required with dosage in the elderly and patients with renal dysfunction (see PRECAUTIONS).

### **Children**

PONSTAN is not recommended for children under 14 years of age.

---

## Contraindications

---

1. Patients showing evidence of chronic inflammation and/or active ulceration of either the upper or lower gastrointestinal tract and patients with pre-existing renal disease.
2. Patients in whom aspirin and/or other NSAIDs have induced symptoms of bronchospasm, allergic rhinitis or urticaria because the potential exists for cross-sensitivity.
3. Patients with impaired renal function or hepatic failure.
4. Patients previously experiencing diarrhoea on taking this drug.
5. Patients who have previously exhibited hypersensitivity to mefenamic acid or any of the components of PONSTAN (see **Description**).
6. Patients with severe heart failure.
7. Treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.
8. Children under 14 years of age.

---

## Warnings and Precautions

---

Should pain not be restricted directly to the time of menses, further investigations to exclude the possibility of pelvic disease are indicated prior to prescribing the drug.

PONSTAN is indicated for primary menorrhagia; therefore, secondary causes of menorrhagia (eg endometriosis) should be excluded before prescribing the drug for this indication.

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

### Cardiovascular Effects

**Cardiovascular Thrombotic Events:** NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal. This risk may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular disease risk factors may be at greater risk. To minimise the potential risk for an adverse cardiovascular event in patients treated with mefenamic acid, especially in patients with cardiovascular risk factors, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs and/or symptoms of serious cardiovascular toxicity and the steps to take if they occur (see CONTRAINDICATIONS).

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with NSAID use.

**Hypertension:** NSAIDs may lead to the onset of new hypertension or worsening of pre-existing hypertension and patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to

patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

**Heart Failure:** Fluid retention and oedema have been observed in some patients taking NSAIDs, including mefenamic acid. Therefore, PONSTAN should be used with caution in patients with compromised cardiac function and other conditions predisposing to or worsened by fluid retention. Patients with pre-existing heart failure or hypertension should be closely monitored.

## **Gastrointestinal Effects**

NSAIDs, including mefenamic acid, can cause serious, potentially fatal gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration and perforation of the stomach, small intestine or large intestine. The frequency of such events may increase with dose or duration of use, but can occur at any time without warning. Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short term therapy is not without risk.

Patients at most risk of developing GI complications with NSAIDs are the elderly, patients with cardiovascular disease, patients using concomitant aspirin, patients with a prior history of, or active, gastrointestinal disease such as ulceration, GI bleeding or inflammatory conditions, and patients with a history of smoking and alcoholism. Therefore mefenamic acid should be used with caution in these patients (see CONTRAINDICATIONS). When GI bleeding or ulceration occurs in patients receiving PONSTAN, the drug should be withdrawn immediately. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

If diarrhoea occurs, PONSTAN should be promptly discontinued. Symptoms may recur in certain patients following subsequent exposure.

## **Severe Skin Reactions**

NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash, mucosal lesion or any other sign of hypersensitivity. If this occurs, the drug should be promptly discontinued.

PONSTAN may cause an exacerbation of chronic urticaria in patients with this disease.

## **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.

## **Renal Effects**

As with other NSAIDs, long-term administration of PONSTAN to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with haematuria, proteinuria, glomerulitis, papillary necrosis and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with pre-renal 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 decomposition. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, nephrotic syndrome, those taking diuretics and the elderly. Such patients should be carefully monitored while receiving PONSTAN.

Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state. Since PONSTAN is eliminated primarily by the kidneys the drug should not be administered to patients with significantly impaired renal functions (see **Contraindications**).

Renal function should be checked periodically.

### **Hepatic Effects**

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

As with other NSAIDs borderline elevations of liver function tests may occur. These elevations may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with mefenamic acid.

Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with other NSAIDs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (eg eosinophilia, rash etc), PONSTAN should be discontinued.

### **Haematologic Effects**

PONSTAN 500 mg and aspirin 650 mg, four times a day, both caused significant further lowering of the prothrombin concentration (PONSTAN 3.48% and aspirin 2.75%) in patients in whom the concentration has been initially lowered by anticoagulant therapy. Caution should therefore be exercised in administering PONSTAN to patients on anticoagulant therapy, such as warfarin, and should not be given when prothrombin concentration is in the range of 10 to 20% of normal. Careful monitoring of blood coagulation factors is recommended (see **Interactions**).

### **Other Effects**

PONSTAN should be used with caution in known asthmatics.

As no data presently exist concerning the effect of PONSTAN, if any, on the efficacy of intrauterine contraceptive devices, physicians should be alert to the possibility of a reduction in contraceptive efficacy, in women with an IUCD taking PONSTAN.

### **Use in Pregnancy: Category C**

NSAIDs inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the foetal ductus arteriosus, foetal renal impairment, inhibition of platelet aggregation, and delay labour and birth. Continuous treatment with NSAIDs during the last trimester of pregnancy should only be given on sound indications. During the last

few days before expected birth, agents with an inhibitory effect on prostaglandin synthesis should be avoided.

It is not known if mefenamic acid 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 mefenamic acid therapy should consult their physician if they decide to become pregnant.

### **Use in Lactation**

Trace amounts of PONSTAN 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.

### **Paediatric Use**

Safety and effectiveness in children below the age of 14 years have not been established.

---

## **Adverse Effects**

---

### **Gastrointestinal disorders**

The most frequently reported adverse effects associated with the use of PONSTAN involve the gastrointestinal tract. In controlled studies for up to eight months, the following disturbances were reported in decreasing order of frequency; diarrhoea (approximately 5% of patients), nausea with or without vomiting, other gastrointestinal symptoms and abdominal pain. In certain patients, the diarrhoea was of sufficient severity to require discontinuation of the medication. The occurrence of the diarrhoea is usually dose related, generally subsides on reduction of dosage and rapidly disappears on termination of therapy.

Other less frequently reported gastrointestinal effects were anorexia, cholestatic jaundice, colitis, enterocolitis, mild hepatic toxicity, hepatitis, hepatorenal syndrome, pyrosis, pancreatitis, steatorrhea, flatulence, constipation and gastrointestinal ulceration with and without haemorrhage.

### **Blood and lymphatic system**

Cases of auto-immune haemolytic anaemia have been associated with the continuous administration of 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 haematocrit have been noted in 2 to 5% of patients and primarily in those who have received prolonged therapy. Leukopenia, eosinophilia, thrombocytopenia purpura, agranulocytosis, pancytopenia, aplastic anaemia and bone marrow hypoplasia have also been reported.

### **Immune system**

Anaphylaxis.

## **Metabolism and nutrition**

Glucose intolerance in diabetic patients, hyponatremia.

## **Psychiatric disorders**

Nervousness.

## **Nervous system**

Aseptic meningitis, convulsions, drowsiness, dizziness, headache, blurred vision and insomnia.

## **Eye and ear disorders**

Eye irritation, reversible loss of colour vision and ear pain.

## **Cardiovascular system**

Hypotension and palpitations.

## **Respiratory and thoracic system**

Asthma and dyspnoea.

## **Skin and subcutaneous tissue disorders**

Angioedema, oedema of the larynx, erythema multiforme, perspiration, Lyell's syndrome (toxic epidermal necrolysis), Stevens-Johnson syndrome, pruritus, urticaria, rash and facial oedema.

## **Renal and urinary disorders**

As with other NSAIDs, 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. Haematuria, dysuria and tubulointerstitial nephritis have also been reported.

---

## **Interactions**

---

***Anticoagulants:*** The concurrent use of NSAIDs and warfarin has been associated with severe, sometimes fatal, haemorrhage.

Mefenamic acid, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation and may prolong prothrombin time in patients on warfarin therapy. Mefenamic acid has been shown to displace warfarin from protein binding sites and may enhance the response to oral anticoagulants.

NSAIDs, such as PONSTAN, should be used in combination with warfarin, only if absolutely necessary. Concurrent administration of PONSTAN with oral anticoagulant drugs requires frequent prothrombin time monitoring.

***Anti-hypertensives including diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II antagonists (AIIA):*** NSAIDs such as mefenamic acid can reduce the efficacy of diuretics and other anti-hypertensive drugs.

In patients with impaired renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of an ACE inhibitor or an AIIA with a cyclo-oxygenase inhibitor can increase the deterioration of the renal function, including the possibility of acute renal failure, which is usually reversible. The occurrence of these interactions should be considered in patients taking mefenamic acid with an ACE inhibitor or 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.

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

**Cyclosporin or Tacrolimus:** Concomitant administration with NSAIDs increases the risk of nephrotoxicity.

**Hypoglycaemic agents:** There have been reports of changes in the effects of oral hypoglycaemic agents in the presence of NSAIDs. Therefore, mefenamic acid should be administered with caution in patients receiving insulin or oral hypoglycaemic agents.

**Lithium:** Mefenamic acid has produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. Thus, when mefenamic acid and lithium are administered concurrently, patients should be observed carefully for signs of lithium toxicity.

**Methotrexate:** Caution is advised when methotrexate is administered concurrently with NSAIDs, including mefenamic acid, because NSAID administration may result in increased plasma levels of methotrexate.

---

## Overdosage

---

Symptoms of overdosage are related to the amount of drug ingested and range from gastrointestinal discomfort and diarrhoea to seizures, acute renal failure, confusional state, vertigo, hallucination, 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.

## Treatment

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.

Contact the National Poisons Centre for current advice on management of an overdose.

---

### **Pharmaceutical Precautions**

---

Store below 30°C.

---

### **Medicine Classification**

---

Prescription medicine – packs of 50 capsules.

Pharmacy-Only Medicine – packs of 20 capsules for the treatment of dysmenorrhoea.

---

### **Package Quantities**

---

Blister pack: 20s

HDPE bottles: 50s

---

### **Further Information**

---

PONSTAN capsules contain the inactive ingredients lactose, titanium dioxide, gelatin, brilliant blue FCF, iron oxide yellow and carbon black.

---

### **Name and Address of Sponsor**

---

Pfizer New Zealand Ltd  
PO Box 3998  
AUCKLAND

Toll Free Number: 0800 736 363

---

### **Date of Preparation**

---

22 December 2011