SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

PONSTAN® CAPSULES

PONSTAN® PAEDIATRIC SUPPOSITORIES

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PONSTAN CAPSULES: 250 mg mefenamic acid per capsule.

Contains sugar (lactose).

PONSTAN PAEDIATRIC SUPPOSITORIES: 125 mg mefenamic acid per suppository.

Excipients with known effect

PONSTAN CAPSULES:

Each PONSTAN CAPSULE contains 77,610 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules

PONSTAN CAPSULES: Yellowish opaque body and light blue opaque top. “Parke-Davis” printed in black on body and cap.

Suppositories

PONSTAN PAEDIATRIC SUPPOSITORIES: Creamy white, bullet-shaped suppositories.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PONSTAN CAPSULES are indicated:

- For the relief of mild to moderate pain in acute and chronic conditions including pain of traumatic, arthritic or muscular origin; primary dysmenorrhoea, headache and dental pain.
- As an anti-pyretic in febrile conditions.
- PONSTAN reduces blood loss in menorrhagia where the menorrhagia is due to ovulatory dysfunctional bleeding. Uterine and other pathology should first be excluded before prescribing PONSTAN CAPSULES for this indication.

PAEDIATRIC SUPPOSITORIES are indicated:

- For the symptomatic treatment of pain and fever in children 6 months to 2 years of age when oral therapy is not possible.

4.2 Posology and method of administration

Posology

Gastric irritation may be reduced by taking PONSTAN during meals. Therapy should not be continued for longer than 7 days.

Use the lowest effective dose for the shortest possible duration of treatment.

For patients who are pregnant or breastfeeding, refer to section 4.3, 4.4. and 4.6.

Adults

500 mg three times per day.

In menorrhagia the dosage is 500 mg three times a day beginning with the onset of menstrual flow and continuing for five days or until cessation of flow, whichever is less.

In primary dysmenorrhoea the dosage is 500 mg three times a day commencing at the onset of period pain and continued for up to three days while the symptoms persist.

Paediatric population

Paediatric Suppositories

Children 6 months to 2 years of age, weighing not less than 10 kg: One suppository to be inserted rectally three times a day at intervals of 6 to 8 hours as needed.

The use of paediatric suppositories every 6 to 8 hours for longer than 24 hours is not recommended.

Method of administration

Capsules

For oral use.

Suppositories

For rectal use.

4.3 Contraindications

- Hypersensitivity to mefenamic acid, other nonsteroidal anti-inflammatory drugs (NSAIDs) with prostaglandin-synthetase inhibiting activity or to any of the excipients of PONSTAN (listed in section 6.1). Because the possibility exists for cross-sensitivity to other NSAIDs, PONSTAN should not be given to patients in whom these medicines induce symptoms of bronchospasm, allergic rhinitis, or urticaria.
- Chronic inflammation of either the upper or lower gastrointestinal tract
- Active or history of recurrent ulcer/haemorrhage/perforations
- History of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including PONSTAN
- Heart failure
- Treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery
- Impaired renal or hepatic function

- Epilepsy
- Pregnant women from 20 weeks or later of gestation and in breastfeeding (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

The use of PONSTAN with concomitant systemic non-aspirin NSAIDs, including cyclooxygenase-2 (COX-2) inhibitors, should be avoided. Concomitant use with one or more systemic NSAIDs may increase frequency of gastrointestinal ulcers and bleeding.

Cardiovascular effects

NSAIDs including PONSTAN may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal. This risk may increase with duration of use. The relative increase of this risk appears to be similar in those with or without known cardiovascular disease or cardiovascular risk factors. However, patients with cardiovascular disease, history of atherosclerotic cardiovascular disease or cardiovascular risk factors may also be at greater risk in terms of absolute incidence, due to their increased rate at baseline. To minimise the potential risk for an adverse cardiovascular event in patients treated with PONSTAN, the lowest effective dose should be used for the shortest duration possible. Medical practitioners 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 section 4.3).

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with PONSTAN therapy. In view of PONSTAN's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

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.

NSAIDs including PONSTAN may lead to the onset of new hypertension or worsening of pre-existing

hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals throughout the course of therapy.

Use with oral anticoagulants

PONSTAN may enhance the effects of oral anticoagulants. The concomitant use of NSAIDs, including PONSTAN, with oral anticoagulants increases the risk of gastrointestinal and non-gastrointestinal bleeding and should be given with caution. Oral anticoagulants include warfarin or coumarin-type and novel oral anticoagulants (e.g. apixaban, dabigatran, rivaroxaban). Anticoagulation/international normalised ratio (INR) should be monitored in patients taking a warfarin or coumarin-type anticoagulant (see section 4.5).

Gastrointestinal effects

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation can occur at any time with or without warning symptoms. The risk of gastrointestinal perforation, ulceration or bleeding (PUBs) is higher with increasing doses of PONSTAN, in patients with a history of ulcers, and the elderly. When gastrointestinal bleeding or ulceration occurs in patients receiving PONSTAN, treatment with PONSTAN should be stopped.

PONSTAN should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn’s disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated.

Patients with cardiovascular disease, patients using concomitant corticosteroids, anti-platelet medicines (such as aspirin), or selective serotonin reuptake inhibitors (SSRIs) and patients ingesting alcohol are also at risk of developing gastrointestinal complications with NSAIDs, including PONSTAN.

Diarrhoea may occur within 24 hours following PONSTAN dosage. When diarrhoea occurs, PONSTAN should be discontinued immediately.

Skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome (SJS),

generalised bullous fixed drug eruption (GBFDE) and toxic epidermal necrolysis (TEN) have been reported. PONSTAN should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome has been reported in patients taking NSAIDs such as PONSTAN. Some of these events have been fatal or life-threatening. DRESS syndrome typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS syndrome may resemble an acute viral infection. 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. If such signs or symptoms are present, discontinue PONSTAN and evaluate the patient immediately.

Other effects

Bronchoconstriction may occur with PONSTAN in asthmatic patients with aspirin sensitivity.

Because of the possibility of cross-sensitivity due to structural relationships which exist among NSAIDs, acute allergic reactions may be more likely to occur in patients who have exhibited allergic reactions to these medicines.

Haemolytic anaemia may develop in patients taking PONSTAN. While this condition is generally reversible, death due to PONSTAN-associated haemolytic anaemia has been reported. Liver function tests must be carried out regularly to monitor elevation of enzymes and bilirubin.

Temporary lowering of the white blood cell count has occurred but does not appear to be dose-related. Blood counts should be performed at regular intervals during long-term administration.

Effects on laboratory tests

PONSTAN and its metabolites may give a false positive reaction to certain urine tests for the presence of bile.

Renal effects

NSAIDs, including PONSTAN, may cause interstitial nephritis, glomerulitis, papillary necrosis and nephrotic syndrome. Toxicity has also been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume. Patients at greatest risk are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of NSAID therapy is typically followed by recovery to the pre-treatment state. Since PONSTAN is eliminated primarily by the kidneys, the medicine should not be administered to patients with impaired renal function (see section 4.3). Caution should be exercised in the administration of PONSTAN to patients suffering from dehydration, particularly the elderly.

Hepatic effects

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

Foetal renal toxicity and premature closure of the foetal ductus arteriosus

Regular use of NSAIDs such as PONSTAN during the third trimester of pregnancy may result in premature closure of the foetal ductus arteriosus *in utero*, and possibly, in persistent pulmonary hypertension of the newborn. If used during pregnancy from 20 weeks of gestation and beyond, NSAIDs such as PONSTAN may cause foetal renal dysfunction which may result in reduction of amniotic fluid volume or oligohydramnios in severe cases. PONSTAN is contraindicated in pregnant women from 20 weeks or later of gestation (see sections 4.3 and 4.6).

Special populations

Elderly

The elderly have an increased frequency of adverse reactions to NSAIDs including PONSTAN, especially gastrointestinal perforation, ulceration and bleeding (PUBs) which may be fatal.

Lactose intolerance

PONSTAN capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Anticoagulants

PONSTAN may enhance the effects of anticoagulants such as warfarin. Patients receiving an anticoagulant medicine concurrently with PONSTAN have had a prolongation of prothrombin time. PONSTAN is contraindicated for patients taking an anticoagulant medicine if careful and continuous monitoring of the levels of prothrombin and Factors VII, IX and X is not available.

Antihypertensives

NSAIDs, such as PONSTAN, can reduce the efficacy of antihypertensive medicines including diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists (AIIA) and beta-blockers.

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

Therefore, the concomitant administration of these medicines 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.

Lithium

Patients receiving lithium concurrently with NSAIDs including PONSTAN, have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. Thus, when PONSTAN and lithium are administered concurrently, patients should be observed carefully for signs of lithium toxicity.

NSAIDs

Use of two or more NSAIDs concomitantly could result in an increase in side effects.

Corticosteroids

Corticosteroids increase risk of gastrointestinal perforation, ulceration or bleeding (PUBs).

Anti-platelet medicines and selective serotonin reuptake inhibitors

Anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs) increase risk of gastrointestinal bleeding.

Aspirin

PONSTAN interferes with the anti-platelet effect of low-dose aspirin, and thus may interfere with aspirin's prophylactic treatment of cardiovascular disease.

Ciclosporin and tacrolimus

Concomitant administration with NSAIDs such as PONSTAN increases the risk of nephrotoxicity.

Hypoglycaemic medicines

There have been reports of changes in the effects of oral hypoglycaemic medicines in the presence of NSAIDs such as PONSTAN. Therefore, PONSTAN should be administered with caution in patients receiving insulin or oral hypoglycaemic medicines.

Methotrexate

Caution is advised when methotrexate is administered concurrently with NSAIDs, including PONSTAN, because NSAID administration may result in increased plasma levels of methotrexate, especially in patients

receiving high doses of methotrexate.

4.6 Fertility, pregnancy and lactation

Pregnancy

PONSTAN is contraindicated in pregnant women from 20 weeks or later of gestation (see section 4.3).

PONSTAN should not be used during the first 20 weeks of pregnancy. If there is a compelling need for NSAID treatment during this time, limit use to the lowest effective dose and shortest duration possible.

The inhibition of prostaglandin synthesis by NSAIDs, including PONSTAN, may adversely affect pregnancy. Epidemiological studies suggest an increased risk of spontaneous abortion and congenital malformation after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss.

Regular use of NSAIDs such as PONSTAN during the third trimester of pregnancy may result in premature closure of the foetal ductus arteriosus *in utero*, and possibly, in persistent pulmonary hypertension of the newborn. The onset of labour may be delayed and its duration increased. It is not known if mefenamic acid or its metabolites cross the placenta. However, because of the effects of medicines in this class (i.e. inhibitors of prostaglandin synthesis) on the foetal cardiovascular system, the use of PONSTAN in pregnant women is not recommended and is contraindicated from 20 weeks or later from gestation (see section 4.3.

Oligohydramnios and neonatal renal impairment

When used during pregnancy in the second or third trimester, NSAIDs, including PONSTAN, may cause foetal renal dysfunction which may result in reduction of amniotic fluid volume or oligohydramnios and, in some cases, neonatal renal impairment. 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. Oligohydramnios is often, but not always, reversible with treatment discontinuation. 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. Pregnant women on PONSTAN should be closely monitored for amniotic fluid volume. Consider ultrasound monitoring of amniotic fluid if treatment extends beyond 48 hours. Discontinue treatment with NSAIDs if oligohydramnios occurs.

Breastfeeding

Mefenamic acid may be present in breast milk therefore PONSTAN should not be taken by nursing mothers as it can be transmitted to the nursing infant. Thus, PONSTAN is contraindicated in nursing mothers considering potential adverse effects on the child (see section 4.3).

Fertility

Based on the mechanism of action, the use of NSAIDs, including PONSTAN, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of NSAIDs, including PONSTAN, should be considered.

4.7 Effects on ability to drive and use machines

The effect of PONSTAN on the ability to drive or operate machinery has not been systematically evaluated. However, adverse effects of PONSTAN include dizziness, drowsiness and blurred vision which could affect the ability to drive or use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Cardiac disorders: Oedema, hypertension and cardiac failure.

Gastrointestinal system disorders: The most commonly observed adverse events are gastrointestinal in nature: peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn’s disease and gastritis have also been reported.

Skin and subcutaneous tissue disorders: Bullous reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Tabulated summary of adverse reactions

System Organ Class	**Frequency**	**Adverse Event**
Blood and lymphatic system disorders	Less frequent	Haemolytic anaemia, decreased haematocrit, leucopenia, eosinophilia, thrombocytopenia or thrombocytopenic purpura, agranulocytosis pancytopenia, aplastic anaemia, bone marrow hypoplasia, platelet aggregation inhibition
Immune system disorders	Less frequent	Anaphylaxis
Metabolism and nutrition disorders	Less frequent	Glucose intolerance in diabetic patients, hyponatremia, fluid retention
Psychiatric disorders	Less frequent	Nervousness
Nervous system disorders	Less frequent	Aseptic meningitis, drowsiness, dizziness, headache, blurred vision, convulsions, insomnia
Eye disorders	Less frequent	Eye irritation, reversible loss of colour vision
Ear and labyrinth disorders	Less frequent	Ear pain
Cardiac disorders	Less frequent	Palpitations

Vascular disorders	Less frequent	Hypotension, hypertension
Respiratory, thoracic and mediastinal disorders	Less frequent	Asthma, bronchospasm, Dyspnoea
Gastrointestinal disorders	Frequent	Diarrhoea, nausea with or without vomiting, abdominal pain
	Less frequent	Anorexia, pyrosis, flatulence, enterocolitis, colitis, steatorrhoea, cholestatic jaundice, hepatitis, pancreatitis, hepatorenal syndrome, mild hepatic toxicity, constipation, gastrointestinal inflammation, gastrointestinal ulceration (with or without gastrointestinal haemorrhage), gastrointestinal perforation
Skin and subcutaneous tissue disorders	Less frequent	Angioedema, oedema of the larynx, Stevens-Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis), erythema multiforme, dermatitis exfoliative, perspiration, pruritis, urticaria, rash, facial oedema
Renal and urinary disorders	Less frequent	Renal failure, papillary necrosis, haematuria, dysuria, tubulointerstitial nephritis, proteinuria, glomerulonephritis, nephrotic syndrome
General disorders and administration site conditions	Less frequent	Oedema
Investigations	Less	Urobilinogen urine (false-positive), abnormal

	frequent	liver function test

Post-marketing experience

System organ class	**Adverse event**
Skin and subcutaneous tissue disorders	Drug Reaction with Eosinophilia, Systemic Symptoms (DRESS) syndrome, and generalised bullous fixed drug eruption (GBFDE) [see section 4.4]

Paediatric population

General disorders and administration site conditions: hypothermia

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

See section 4.8.

PONSTAN has a marked tendency to induce tonic-clonic (grand mal) convulsions in overdosage. Dyskinesia, acute renal failure, confusional state, vertigo, hallucination and coma have been reported. Overdose has led to fatalities.

Treatment is symptomatic and supportive. Following accidental overdosage, the stomach should be emptied immediately by inducing emesis followed by administration of activated charcoal. Vital functions should be monitored and supported. Haemodialysis is of little value since PONSTAN and its metabolites are firmly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.7 Anti-pyretic or anti-pyretic and anti-inflammatory analgesics

Mechanism of action

Mefenamic acid has analgesic, anti-inflammatory and anti-pyretic properties.

The pharmacological activity of mefenamic acid may be due in part to its ability to inhibit the synthesis of prostaglandins. Mefenamic acid also inhibits the action of exogenous prostaglandins on uterine muscle, uterine tube contraction and ovarian cyclic AMP and progesterone formation in animal models.

5.2 Pharmacokinetic properties

Absorption

Mefenamic acid is well absorbed from the gastrointestinal tract. Peak plasma concentrations occur in about 2 to 4 hours, with a half-life of 2 to 4 hours. Plasma levels are proportional to dose, following multiple doses, with no medicine accumulation.

Distribution

Mefenamic acid is extensively bound to plasma proteins.

Metabolism

Mefenamic acid metabolism is predominantly mediated via cytochrome P450 CYP 2C9 in the liver. Patients who are known or suspected to be poor CYP2C9 metabolisers based on previous history/experience with other CYP2C9 substrates, should be administered mefenamic acid with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Elimination

Over 50 % of the dose may be recovered in the urine as unchanged medicine or conjugated metabolites.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

PONSTAN CAPSULES

Capsule content

Gelatin

Lactose

Sodium lauryl sulphate

Capsule shell

Gelatin

Indigo carmine (indigotine) (E132)

Titanium dioxide (E171)

Yellow iron oxide (E172)

Printing ink

Black iron oxide (E172)

PONSTAN PAEDIATRIC SUPPOSITORIES

Hard fat (Suppocire AML)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PONSTAN CAPSULES

36 months

PONSTAN PAEDIATRIC SUPPOSITORIES

24 months

6.4 Special precautions for storage

Store in a cool (at or below 25 ºC), dry place.

6.5 Nature and contents of container

PONSTAN CAPSULES: White PVC/Aluminium blister strips each containing 10 capsules packed into a carton.

Each carton contains 20 capsules.

PONSTAN PAEDIATRIC SUPPOSITORIES: Packs of 5.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBERS

PONSTAN CAPSULES: B/2.7/560

PONSTAN PAEDIATRIC SUPPOSITORIES: 27/2.7/0561

9. DATE OF FIRST AUTHORISATION

PONSTAN Capsules 250 mg: 16 November 1993

PONSTAN Paediatric Suppositories 125 mg: 01 December 1993

10. DATE OF REVISION OF THE TEXT

30 April 2024

BOTSWANA: S2 Capsules: Reg. No.: B9321805
NAMIBIA: S2 Capsules: Reg. No.: 04/2.7/1237 Paediatric Suppositories: Reg. No.: 04/2.7/1238
ZAMBIA: P Capsules: Reg. No.: 120/027 Paediatric Suppositories: Reg. No.: 120/028
ZIMBABWE: PP Capsules: Reg. No. 74/2.1/261