SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

PONAC FORTE 500 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 500 mg of mefenamic acid.

Contains sugar: Lactose monohydrate 143,00 mg per tablet.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

Off-white, film coated concave tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indication

PONAC FORTE is indicated for the treatment of post traumatic conditions such as pain, swelling and inflammation, for a maximum period of five (5) days. PONAC FORTE is also indicated as treatment of primary dysmenorrhoea, subject to a maximum daily dose of 500 mg three (3) times a day for a maximum of three (3) days.

4.2 Posology and method of administration

Posology

Adults

Use the lowest effective dose for the shortest possible duration of treatment. PONAC FORTE must be taken with meals.

Relief of mild to moderate pain: 500 mg three (3) times a day.

Acute pain: an initial dosage of 500 mg, thereafter 250 mg every six (6) hours for a maximum treatment period of five (5) days.

Primary dysmenorrhoea: a maximum daily dose of 500 mg three (3) times a day and a maximum treatment period of three (3) days.

Method of administration

Oral use only.

4.3 Contraindications

PONAC FORTE is contraindicated in patients:

- With hypersensitivity to mefenamic acid or any of the excipients of PONAC FORTE (see section 6.1).
- With hypersensitivity to non-steroidal anti-inflammatory agents, with prostaglandin synthetase inhibiting activity. Since the possibility of cross-sensitivity among non- steroidal anti-inflammatory agents exists, PONAC FORTE should not be given to patients in whom these medicines induce symptoms of bronchospasm, allergic rhinitis, or urticaria.
- With a history of gastrointestinal perforation, ulceration, or bleeding (PUBs) related to previous NSAIDs (including PONAC FORTE) and/or an active or history of recurrent peptic and/or intestinal ulceration/haemorrhage/perforations.
- With chronic inflammation of either the upper or lower gastrointestinal tract.
- Who suffer from epilepsy (see section 4.4).

- With impaired hepatic or renal function (see section 4.4).
- With heart failure (see section 4.4).
- Requiring treatment for pain after coronary artery bypass graft (CABG) surgery.
- Pregnancy (from 20 weeks or later of gestation) and lactation (see section 4.6).
- With the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance (see section 4.4).

4.4 Special warnings and precautions for use

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

Patients on prolonged therapy with PONAC FORTE should be kept under regular surveillance with particular attention to liver dysfunction, rash, blood dyscrasias or development of diarrhoea. Appearance of any of these symptoms should be regarded as an indication to stop therapy immediately.

Precaution should be taken in patients suffering from dehydration and renal disease, particularly the elderly.

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

Blood counts and liver function should be monitored during long-term therapy with PONAC FORTE. PONAC FORTE may enhance the effects of warfarin (see section 4.5).

PONAC FORTE tablets contain lactose monohydrate which may have an effect on the glycaemic control of patients with diabetes mellitus.

Special Populations

Elderly

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

The risk of gastrointestinal perforation, ulceration, and bleeding (PUBs) is higher with increasing doses of PONAC FORTE, in patients with a history of ulcers and the elderly. PONAC FORTE should be avoided in elderly patients with dehydration or pre-existing renal disease.

Respiratory disorders

Caution is required if administered to patients suffering from, or with a previous history of bronchial asthma since NSAIDs such as PONAC FORTE may precipitate bronchospasm in such patients. Bronchoconstriction may occur with PONAC FORTE in asthmatic patients with aspirin sensitivity.

Cardiovascular, renal and hepatic impairment

The administration of PONAC FORTE may cause a dose-dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of

this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly, see section 4.3. PONAC FORTE may enhance the effects of warfarin.

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.

Liver function tests must be carried out regularly to monitor elevation of enzymes and bilirubin.

Cardiovascular and cerebrovascular effects

Caution is required in patients with a history of hypertension as fluid retention and oedema have been reported in association with PONAC FORTE therapy. In view of PONAC FORTE's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients, see section 4.3.

Caution is required in patients with significant risk factors for cardiovascular events (e.g., hypertension, hyperlipidaemia, diabetes mellitus, smoking) and should only be treated with diclofenac after careful consideration.

Appropriate monitoring and advice are required for patients with a history of hypertension, as fluid retention and oedema have been reported in association with NSAID therapy such as PONAC FORTE.

Patients with uncontrolled hypertension, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with PONAC FORTE after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g., hypertension, hyperlipidaemia, diabetes mellitus, smoking).

As NSAIDs such as PONAC FORTE can interfere with platelet function, they should be used in caution in patients with intracranial haemorrhage and bleeding diathesis.

Gastrointestinal bleeding, ulceration, and perforation

When gastrointestinal perforation, ulceration or bleeding occurs in patients receiving PONAC FORTE, treatment with PONAC FORTE should be stopped, see section 4.3.

PONAC FORTE 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.

Gastrointestinal perforation, ulceration, or bleeding (PUB) which can be fatal, has been reported with all NSAIDs such as PONAC FORTE at any time during treatment, with or without warning symptoms, or a previous history of serious gastrointestinal events. Smoking and alcohol use are added risk factors.

The risk of gastrointestinal perforation, ulceration or bleeding is higher with increasing doses of PONAC FORTE and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly.

Combination therapy with protective agents (e.g., misoprostol or proton pump inhibitors) should be considered for patients at risk of gastrointestinal bleeding such as the elderly and also for patients requiring concomitant low dose aspirin, or other medicines likely to increase gastrointestinal risk.

Patients with a history of gastrointestinal toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial stages of PONAC FORTE treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of gastrointestinal side effects or bleeding such as corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors or anti-platelet agents such as aspirin.

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

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 of PONAC FORTE.

SLE and mixed connective tissue disease

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis.

Dermatological effects

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Steven-Johnson syndrome, and toxic epidermal necrolysis, have been reported. PONAC FORTE should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment.

Cross-sensitivity

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

Occurrence of rash is a definite reason for stopping PONAC FORTE because exfoliative dermatitis has been reported on continued use after development of a rash.

Dysmenorrhoea

In dysmenorrhoea lack of response should alert the medical practitioner to investigate other causes.

Poor CYP2C9 metabolisers

In patients who are known or suspected to be poor CYP2C9 metabolisers based on previous history/experience with other CYP2C9 substrates, PONAC FORTE should be administered with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Hypokalaemia and renal tubular acidosis

Severe hypokalaemia and renal tubular acidosis have been reported due to prolonged use of NSAIDs as in PONAC FORTE at higher than recommended doses. This risk is increased with the use of codeine/ mefenamic acid as patients may become dependent on the codeine component (section 4.8 c) Description of selected adverse reactions and section 4.9). Presenting signs and symptoms included reduced level of consciousness and generalised weakness. Mefenamic acid induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

Lactose/galactose intolerance

PONAC FORTE contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g., galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take PONAC FORTE.

4.5 Interaction with other medicines and other forms of interaction

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

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

Anti-coagulants: PONAC FORTE may enhance the effects of anti-coagulants such as warfarin see section 4.4). Patients taking anti-coagulant medicine concurrently with PONAC FORTE have had a prolongation of prothrombin time. PONAC FORTE are contraindicated for patients taking an anticoagulant medicine if careful and continuous monitoring of the levels of prothrombin Factors VII, IX and X is not available.

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

Lithium: Patients receiving lithium concurrently with non-steroidal anti-inflammatory medicines, including PONAC FORTE, have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. Thus, when PONAC FORTE and lithium are administered concurrently, patients should be observed carefully for signs of lithium toxicity.

4.6 Fertility, pregnancy, and lactation

Fertility

The use of PONAC FORTE may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of PONAC FORTE should be considered.

Pregnancy

PONAC FORTE is contraindicated in pregnant women from 20 weeks or later of gestation. (See section 4.3).

Regular use of non-steroidal anti-inflammatory medicines, such as PONAC FORTE, 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 new-born. The onset of labour may be delayed, and its duration increased.

When used during pregnancy in second or third trimester, NSAIDs, including PONAC FORTE, may cause foetal renal dysfunction which may result in reduction of amniotic fluid volume or oligohydramnios in severe cases. Such effects may occur shortly after treatment initiation. Pregnant women on PONAC FORTE should be closely monitored for amniotic fluid volume.

Breastfeeding

Trace amounts of mefenamic acid may be present in breast milk and transmitted to the breastfeeding infant. Therefore, PONAC FORTE should not be taken by mothers breastfeeding their infants.

4.7 Effects on ability to drive and use machines

PONAC FORTE may affect the mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision since PONAC FORTE may cause adverse reactions such as dizziness, drowsiness, fatigue, and visual disturbances. Therefore, patients should not drive, use machinery, or participate in dangerous activities until they are

certain that PONAC FORTE does not adversely affect their ability to do so safely (see section 4.8).

4.8 Undesirable effects

a) Summary of adverse effects

The most commonly observed adverse events with PONAC FORTE are gastrointestinal in nature.

b) Tabulated summary of adverse reactions

Frequencies defined as frequent, less frequent and frequency unknown.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Gastrointestinal disorders	Frequent	Diarrhoea Nausea with or without vomiting Abdominal pain
	Less frequent	Anorexia Pyrosis Flatulence Enterocolitis Colitis Steatorrhea Cholestatic jaundice Hepatitis Pancreatitis

		Hepato-renal syndrome Mild hepatic toxicity Constipation Peptic ulceration, perforation with or without gastrointestinal haemorrhage (sometimes fatal)
	Frequency unknown	Dyspepsia Melaena Haematemesis Ulcerative stomatitis Exacerbation of colitis and Chron's disease Gastritis
Blood and lymphaticsystem disorders	Less frequent	Haemolytic anaemia Decreased haematocritLeukopenia Eosinophilia Thrombocytopenia or Thrombocytopenic purpura, Agranulocytosis Pancytopenia Aplastic anaemia Bone marrow aplasia

Immune system disorders	Less frequent	Acute hypersensitivity reactions (urticaria, bronchospasm, anaphylaxis)
Metabolism and nutrition disorders	Less frequent	Glucose intolerance in diabetic patients Hyponatraemia
	Frequency unknown	Hypokalaemia*
Psychiatric disorders	Less frequent	Nervousness
Nervous system disorders	Less frequent	Drowsiness Dizziness Headache Visual disturbances Convulsions Insomnia
Eye disorders	Frequency unknown	Visual disturbances
Ear andlabyrinth disorders	Less frequent	Ear pain
Cardiac disorders	Less frequent	Palpitations Oedema Hypertension Cardiac failure
Vascular disorders	Less frequent	Hypotension

Respiratory, thoracic and mediastinal disorders	Less frequent	Asthma may be precipitated Bronchospasm Dyspnoea
Skin and subcutaneous tissue disorders	Less frequent	Angioedema Oedema of the larynx Steven-Johnson syndrome Lyell's syndrome (toxic epidermal necrolysis) Erythema multiforme Perspiration Pruritis Urticaria Skin rash Facial oedema
	Frequency unknown	Bullous reactions
Renal and urinary disorders	Less frequent	Renal failure Papillary necrosis Acute interstitial nephritis with haematuria Dysuria Proteinuria Allergic glomerulonephritis
	Frequency unknown	Nephrotic syndrome, elevation in blood urea Renal tubular acidosis

c) Description of Selected Adverse Reactions

* Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of the NSAID component at higher than recommended doses, usually due to dependence on the codeine component of a co-formulation.

Reporting of suspected adverse events

Reporting suspected adverse reactions after authorisation of medicine is important. It allows continued monitoring of the benefit/risk balance of 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/

4.9 Overdose

Mefenamic acid such as in PONAC FORTE has a marked tendency to induce tonic-clonic (grand mal) convulsions in overdosage. Dyskinesia, acute renal failure and coma have been reported. Overdose has led to fatalities.

Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8).

Treatment is symptomatic and supportive. Vital functions should be monitored and supported. Haemodialysis is of little value since mefenamic acid and its metabolites are firmly bound to plasma proteins.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Mefenamic acid, M01AG01

Pharmacological classification: A 2.7 Antipyretic and anti-inflammatory analgesic

Mefenamic acid is a non-steroidal anti-inflammatory medicine (NSAIDs) with antipyretic and analgesic properties. It has central as well as peripheral analgesic actions. Mefenamic acid inhibits cyclo-oxygenase non-selectively and thereby antagonises certain effects of prostaglandins in analgesia.

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. Accumulation does not occur following repeated doses.

Distribution

Mefenamic acid is extensively bound to plasma proteins.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose Sodium (Ac-Di-Sol)

Lactose Monohydrate

Povidone K25

Purified Talc

Magnesium stearate

Opadry II yellow

Polyvinyl alcohol – part. hydrolysed

Titanium dioxide

Macrogol/PEG

Talc

Iron oxide yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a cool dry place at or below 25 °C.

Keep the blisters in the carton until required for use.

Keep in the original container.

Protect from light.

6.5 Nature and contents of container

PONAC FORTE tablets are either packed in a PP container with LDPE closure cap with foam insert and silica gel sachet or in blister packs (foil and blister PVC).

Pack size: 10’s.

Not all packs may be marketed.

6.6 Special precautions for disposal and other handling

No special precautions are required.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Pharmacorp (Pty) Ltd

29 Victoria Link

Route 21 Corporate Park

Irene, 0178

South Africa

8 REGISTRATION NUMBER

Y/2.7/158

9 DATE OF FIRST AUTHORISATION

30 July 1991

10 DATE OF REVISION OF THE TEXT

28 September 2023