1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

PANAMOR - 75 SR TABLETS

PANAMOR - 100 SR TABLETS

PANAMOR-75 INJECTION

PANAMOR SUPPOSITORIES-12,5

PANAMOR SUPPOSITORIES-25

PANAMOR SUPPOSITORIES 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PANAMOR-75 INJECTION

Each 3,0 ml ampoule of PANAMOR-75 INJECTION contains 75,0 mg diclofenac sodium.

Preservative:

Benzyl alcohol 4,0 % *v/v*

Contains sugar: Mannitol 18 mg

PANAMOR SUPPOSITORIES-12,5

Each suppository of PANAMOR SUPPOSITORIES-12,5 contains 12,5 mg diclofenac sodium.

PANAMOR SUPPOSITORIES-25

Each suppository of PANAMOR SUPPOSITORIES-25 contains 25,0 mg diclofenac sodium.

PANAMOR SUPPOSITORIES

Each suppository of PANAMOR SUPPOSITORIES contains 100,0 mg diclofenac sodium.

PANAMOR - 75 SR TABLETS

Each tablet of PANAMOR - 75 SR TABLETS contains 75,0 mg diclofenac sodium.

Sugar free

PANAMOR - 100 SR TABLETS

Each tablet of PANAMOR - 100 SR TABLETS contains 100,0 mg diclofenac sodium.

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

PANAMOR-75 INJECTION: Injection

PANAMOR - 75 SR TABLETS, PANAMOR - 100 SR TABLETS: Tablets

PANAMOR SUPPOSITORIES-12,5, PANAMOR SUPPOSITORIES-25, PANAMOR SUPPOSITORIES: Suppositories

PANAMOR - 75 SR TABLETS is a pink film-coated, triangular tablet.

PANAMOR - 100 SR TABLETS is a pale red, film-coated, round biconvex tablet.

PANAMOR-75 INJECTION is a clear, colourless to slight straw-coloured solution in 3 ml amber ampoules.

PANAMOR SUPPOSITORIES-12,5 is a white, torpedo-shaped suppository.

PANAMOR SUPPOSITORIES-25 is a white, torpedo-shaped suppository.

PANAMOR SUPPOSITORIES is a large, white, torpedo-shaped suppository.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PANAMOR is indicated for:

- Treatment of post-traumatic pain and inflammation.
- Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, ankylosing spondylitis, osteoarthrosis and spondylarthritis. Painful musculoskeletal conditions.
- Non-articular rheumatism.
- Mild to moderately painful post-operative and post-traumatic inflammation and swelling, pain following dental surgery.
- Symptomatic treatment of primary dysmenorrhoea.

PANAMOR-75 INJECTION used for intramuscular injection is indicated for:

- Initial therapy for inflammatory and degenerative rheumatic diseases as well as for the treatment of mild to moderately painful conditions due to inflammation of non-rheumatic origin.

PANAMOR -75 INJECTION used for the preparation of intravenous infusion is indicated for:

- Treatment or prevention of post-operative mild to moderate pain of inflammatory origin in the absence of any infection.

PANAMOR SUPPOSITORIES is indicated for:

- Painful post-operative and post-traumatic inflammation and swelling.

4.2 Posology and method of administration

Posology

As a general recommendation, the dose should be individually adjusted.

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

Adults

PANAMOR - 75 SR TABLETS and PANAMOR - 100 SR TABLETS:

As a rule, the initial daily dosage is 100 mg to 150 mg administered as one tablet of PANAMOR

- 100 SR TABLETS as a single dose, or two tablets of PANAMOR - 75 SR TABLETS taken in two divided doses. In milder cases, as well as for long-term therapy, one tablet of PANAMOR - 75 SR TABLETS is usually sufficient.

PANAMOR-75 INJECTION:

75 mg by deep intragluteal injection once daily, or two times daily, in severe or hospitalised cases, each injection should be separated by an interval of a few hours (one into each buttock).

PANAMOR-75 INJECTION should not be given for more than two days; if necessary, the treatment can be continued with PANAMOR tablets or suppositories (see section 4.4).

Two alternative dosage regimens of infusion are recommended:

- For the *treatment* of moderate to severe postoperative pain, 75 mg should be infused continuously over a period of 30 minutes to 2 hours. If necessary, treatment may be repeated, but a total dosage of 150 mg within any period of 24 hours must not be exceeded.
- For the *prevention* of postoperative pain, a loading dose of 25 mg to 50 mg should be infused after surgery over 15 minutes to 1 hour, followed by a continuous infusion of approximately 5 mg per hour up to a maximum daily dosage of 150 mg.

PANAMOR-100 mg suppositories:

The average adult dose is 100 mg daily.

To suppress nocturnal pain and morning stiffness, treatment with tablets during the day can be supplemented by the administration of one PANAMOR SUPPOSITORIES at bedtime, up to a maximum dosage of 150 mg daily.

Paediatric population

PANAMOR-12,5 mg and PANAMOR-25 mg suppositories:

Children aged 2 years or more should be given 2 mg to 3 mg per kg body mass daily, in two or three fractional doses.

The following dosage strengths are not suitable for use in children and adolescents below 14 years of age:

- PANAMOR-75 SR TABLETS
- PANAMOR-100 SR TABLETS
- PANAMOR-75 INJECTION
- PANAMOR SUPPOSITORIES (100 mg)

Method of administration

PANAMOR -75 SR TABLETS and PANAMOR-100 SR TABLETS: Oral administration

PANAMOR-75 INJECTION: Intramuscular injection; used for the preparation of intravenous infusion

SUPPOSITORIES-12,5; PANAMOR SUPPOSITORIES-25; PANAMOR SUPPOSITORIES: Rectal administration

PANAMOR SR TABLETS: The tablets should be swallowed whole with a glass of water. These tablets should be neither broken nor chewed and should preferably be taken at

mealtimes. Where the symptoms are most pronounced during the night or in the morning, PANAMOR - 100 SR TABLETS should be taken in the evening.

PANAMAMOR-75 INJECTION

Each injection must be given at a different site. Not to be given by intravenous injection.

Intramuscular injection:

The following directions for intramuscular injection must be followed in order to avoid damage to a nerve or other tissue at the injection site.

Only for deep intragluteal injection into the upper outer quadrant.

After inserting the needle the plunger should be pulled back to avoid inadvertent intra-arterial injection.

PANAMOR -75 INJECTION should not be mixed with other injection solutions.

Alternatively, it is possible to combine one ampoule of PANAMOR-75 INJECTION, with a diclofenac tablet, such as PANAMOR, up to a maximum daily dosage of 150 mg.

PANAMOR -75 INJECTION *used for the preparation of intravenous infusion:*

PANAMOR -75 INJECTION must not be given as an intravenous bolus injection and must not be mixed with other injection solutions. Infusion solutions of sodium chloride 0,9 % or glucose 5 % without sodium bicarbonate as an additive present a risk of supersaturation, possibly leading

to formation of crystals or precipitates. Only clear solutions should be used. If crystals or precipitates are observed, the infusion solution should not be used.
Do not use infusion solutions other than those recommended (for instructions on dilution of the product before administration see section 6.6).

PANAMOR-75 INJECTION infusion should not be given for more than 2 days; if necessary, treatment to be continued with diclofenac tablets or suppositories, such as PANAMOR.

PANAMOR SUPPOSITORIES
Not to be taken by mouth, as per rectal use only. The suppositories should be inserted well into the rectum. It is recommended to use the suppositories after passing stools.

Suppositories should never be divided for administration or stored under incorrect storage conditions as this may lead to an uneven distribution of active medicine in the suppository (see section 6.4).

Do not use suppositories deformed by exposure to temperatures above 30 °C.

4.3 Contraindications

PANAMOR is contraindicated in:

- Patients with hypersensitivity to diclofenac or to any excipients in PANAMOR (see section 6.1).
- Asthmatic patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or by other NSAIDs.

- Patients with porphyria.
- Children under the age of two years.
- Patients with a history of active gastrointestinal bleeding, ulceration or perforation (PUBs) related to previous NSAIDs, or peptic ulceration (see section 4.4).
- Active or history of recurrent ulcer/haemorrhage/perforations.
- Hepatic or renal failure (see section 4.4).
- Patients sensitive to any other non-steroidal anti-inflammatory medicine.
- Heart failure; established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease.
- Pregnant women from around 30 weeks of gestation and later in pregnancy due to the risks of oligohydramnios/ foetal renal dysfunction and premature closure of the foetal ductus arteriosus (see section 4.4 and 4.6).
- Lactation.

PANAMOR-75 INJECTION is contraindicated in*:*

The intravenous use of PANAMOR -75 INJECTION is absolutely contraindicated in patients with impaired renal function and/or any form of shock.

- The intravenous use in children is contraindicated due to insufficient evidence.
- Patients with known sensitivity to sodium metabisulphite.

PANAMOR SUPPOSITORIES additionally is contraindicated in:

- Proctitis.

4.4 Special warnings and precautions for use

General

Use the lowest effective dose for the shortest possible duration of treatment (see section 4.2). Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

Allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in cases without earlier exposure to diclofenac, as in PANAMOR (see section 4.8).

Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to diclofenac, as in PANAMOR.

PANAMOR may mask the signs and symptoms of infection due to its pharmacodynamic properties.

Serious interactions have been reported after the use of high dose methotrexate with diclofenac, as in PANAMOR (see section 4.5).

Cardiovascular and cerebrovascular effects

Caution is required in patients with a history of hypertension and/or heart failure.

As the cardiovascular risks of diclofenac, as in PANAMOR, may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should

be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically (see section 4.4).

Appropriate monitoring and advice are required for patients with a history of hypertension and congestive heart failure (NYHA-I) including diclofenac, as in PANAMOR (see section 4.3).

Data consistently point towards increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, as in PANAMOR, particularly at high dose (150 mg daily).

Patients should remain alert for the signs and symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings. Patients should be instructed to see a medical practitioner immediately in case of such an event.

In view of PANAMOR's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

Elderly

There are generally more serious consequences in the elderly. PANAMOR should be used with care as the elderly has an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforations (PUBs), which may be fatal.

The risk of GI bleeding is higher with increasing PANAMOR doses and in patients with a

history of ulcers, particularly if complicated with haemorrhage or perforation and in the elderly (see section 4.3).

Caution is indicated in the elderly on basic medical grounds. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.

Gastrointestinal effects

Gastrointestinal bleeding (haematemesis, melaena), ulceration or perforation, which can be fatal, have been reported with diclofenac, as in PANAMOR and may occur at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events.

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose.

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding). Caution is recommended in patients receiving concomitant medicines which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, anti-platelet medicines or selective serotonin-reuptake inhibitors (see section 4.5).

Close medical surveillance is imperative and particular caution should be exercised when prescribing PANAMOR in patients with symptoms indicative of gastrointestinal (GI) disorders or

with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see section 4.8).

Close medical surveillance and caution should also be exercised in patients with patients with gastrointestinal disease and a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as their condition may be exacerbated (see section 4.8).

When gastrointestinal bleeding or ulceration occurs in patients receiving PANAMOR, treatment with PANAMOR should be stopped.

Combination therapy with protective medicines (e.g. proton pump inhibitors or misoprostol) should be considered for these patients, and also for patients requiring concomitant use of medicines containing low-dose acetylsalicylic acid (aspirin) or other medicines likely to increase gastrointestinal risk (see section 4.5).

NSAIDs, including diclofenac, as in PANAMOR, may be associated with increased risk of GI anastomotic leak. Close medical surveillance and caution are recommended when using diclofenac, as in PANAMOR, after GI surgery.

Serious skin reactions

Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) have been reported. PANAMOR should

be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity (see section 4.8).

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.

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as PANAMOR. Some of these events have been fatal or life-threatening. DRESS 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 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 PANAMOR and evaluate the patient immediately.

Pregnancy

It is recommended that PANAMOR is avoided in pregnant women at 20 weeks or later in pregnancy (see section 4.3 and 4.6).

Avoid prescribing NSAIDs, such as diclofenac as in PANAMOR, at 30 weeks and later in pregnancy because of the additional risk of premature closure of the foetal ductus arteriosus (see section 4.6)

The use of NSAIDs, such as diclofenac, as in PANAMOR, around 20 weeks gestation or later

in pregnancy may cause foetal renal dysfunction leading to 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 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 NSAID treatment is necessary between 20 weeks and 30 weeks gestation, limit PANAMOR use to the lowest effective dose and shortest duration possible.

Healthcare professionals should consider ultrasound monitoring of amniotic fluid if PANAMOR treatment extends beyond 48 hours. Discontinue PANAMOR if oligohydramnios occurs and follow up according to clinical practice.

Pre-existing asthma

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions to PANAMOR like asthma exacerbations, (so-called intolerance to analgesics/ analgesics-asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other medicines, e.g. with skin reactions, pruritus or urticaria see section 4.3)

Hepatic impairment

Close medical surveillance is required when prescribing PANAMOR to patients with impaired hepatic function, as their condition may be exacerbated.

As with diclofenac, as in PANAMOR, values of one or more liver enzymes may increase. During prolonged treatment with PANAMOR, regular monitoring of hepatic function is indicated as a precautionary measure.

It is advisable to perform blood counts in patients undergoing prolonged treatment.

If abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (eosinophilia, rash), PANAMOR should be discontinued. Hepatitis may occur with PANAMOR without prodromal symptoms.

Renal effects

As fluid retention and oedema have been reported in association with PANAMOR therapy, particular caution is called for in patients with impaired cardiac or renal function**,** history of hypertension**,** the elderly, patients receiving concomitant treatment with diuretics or medicines that can significantly impact renal function, and in those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery (see section 4.3). Monitoring of renal function is recommended as a precautionary measure when using PANAMOR in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

Haematological effects

During prolonged treatment with PANAMOR, monitoring of the blood count is recommended.

Diclofenac, as in PANAMOR may reversibly inhibit platelet aggregation, decreased platelet aggregation with increased bleeding time may occur (see section 4.5). Patients with defects of haemostasis bleeding diathesis or haematological abnormalities should be carefully monitored.

Anaemia may occur as a result of water retention or effects on erythropoiesis. Consequently, it is advisable to monitor the levels of haemoglobin and haematocrit if symptoms of anaemia are detected. Hyperpotassemia may occur in diabetic patients or those who are also taking potassium-sparing medicines (see section 4.5).

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 (see section 4.8).

Female fertility

The use of PANAMOR may impair female fertility and is not recommended in women attempting to conceive. In women who may have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of PANAMOR should be considered (see section 4.6).

PANAMOR -75 INJECTION:

Nicolau syndrome

There is a risk of Nicolau syndrome when using diclofenac, as in PANAMOR-75 INJECTION.

Injection site reactions have been reported after the administration of PANAMOR-75 INJECTION, including injection site necrosis and embolia cutis medicamentosa, also known as Nicolau Syndrome (particularly after inadvertent subcutaneous administration).

Administration

PANAMOR -75 INJECTION must be carried out following strict rules of asepsis and antisepsis (see section 4.2).

The instructions for intramuscular injection should be strictly followed in order to avoid undesirable effects at the injection site, which may result in muscle weakness, muscle paralysis, hypoaesthesia and injection site necrosis (see section 4.2 and 4.8).

Duration of treatment

PANAMOR-75 INJECTION must not be administered for longer than 2 days. After 2 days, the need for an alternative NSAID should be reviewed and if long-term treatment with an NSAID is required, patients should be monitored for evidence of renal and hepatic dysfunction and blood count abnormalities. This is particularly important in the elderly.

Paediatric population

The following dosage strengths are not suitable for use in children and adolescents below 14 years of age (see section 4.2):

- PANAMOR-75 SR TABLETS
- PANAMOR-100 SR TABLETS
- PANAMOR-75 INJECTION

- PANAMOR SUPPOSITORIES (100 mg)

Excipients

PANAMOR -75 INJECTION

PANAMOR-75 INJECTION contains mannitol, that may cause a mild laxative effect.

PANAMOR -75 INJECTION contains sodium metabisulphite. Special caution is recommended when used parenterally especially in patients with bronchial asthma because symptoms may be exacerbated. The presence of sodium metabisulphite can, lead to hypersensitivity reactions, which may manifest as an acute asthma attack, clouding of consciousness, or shock (see section 4.3).

PANAMOR-75 INJECTION contains benzyl alcohol as a preservative.

Increased risk due to accumulation in young children.

High volumes should be used with caution and only if necessary, especially in patients with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

4.5 Interaction with other medicines and other forms of interaction

NSAIDs including cyclo-oxygenase-2 selective inhibitors:

Concurrent use of two or more NSAIDs, could result in an increase in undesirable effects.

The concomitant use of PANAMOR with other systemic NSAIDs including cyclooxygenase-2 selective inhibitors, should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects.

NSAIDs, corticosteroids and acetylsalicylic acid (aspirin)

Concomitant administration of diclofenac as in PANAMOR and other systemic NSAIDs, corticosteroids or acetylsalicylic acid (aspirin) may increase the frequency of gastrointestinal undesirable effects (see section 4.4) and is not recommended.

Increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs). Concomitant administration of glucocorticoids or other non-steroidal anti-inflammatory medicines may aggravate gastrointestinal undesirable effects.

Lithium

If used concomitantly, PANAMOR may raise plasma concentrations of lithium. NSAIDs, such as PANAMOR have been reported to increase blood lithium levels via decreased renal excretion of lithium. If this combination is considered necessary, lithium plasma concentrations should be monitored carefully during the initiation, adjustment and withdrawal of diclofenac, as in PANAMOR treatment.

Digoxin

If used concomitantly, PANAMOR may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

Diuretics and antihypertensive medicines

Concomitant use of PANAMOR with diuretics or antihypertensive medicines (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin-II antagonists and

medicines that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated, and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity.

Medicines known to cause hyperkalemia

Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently (see section 4.4).

Anticoagulants and anti-platelet medicines:

The bioavailability of PANAMOR is reduced by acetylsalicylic acid (aspirin), and that of acetylsalicylic acid (aspirin) by PANAMOR, when the two medicines are administered together. Caution is recommended since concomitant administration could increase the risk of bleeding.

There are reports of an increased risk of haemorrhage in patients receiving PANAMOR and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Anticoagulants and heparin (administered in the elderly or at curative doses):

Caution is recommended since concomitant administration with NSAIDs, such as PANAMOR, could increase the risk of bleeding via inhibition of platelet function and damage to the gastroduodenal mucosa (see section 4.4). NSAIDs, such as PANAMOR, may enhance the effects of anticoagulants such as warfarin and heparin. Heparin is not recommended for administration to elderly patients or at curative doses. Careful monitoring of the international normalized ratio (INR) is required if co-administration cannot be avoided. Although clinical investigations do not appear to indicate that diclofenac, as in PANAMOR, affects the action of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac, as in PANAMOR , and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended. As with other NSAIDs, diclofenac, as in PANAMOR in high dose can reversibly inhibit platelet aggregation.

Thrombolytics and anti-platelet medicines:

Caution is recommended since concomitant administration with NSAIDs, such as PANAMOR, could cause increased risk of bleeding via inhibition of platelet function and damage to the gastroduodenal mucosa.

Selective serotonin reuptake inhibitors (SSRIs):

Concomitant administration of systemic NSAIDs, such as PANAMOR and SSRIs may increase the risk of gastrointestinal bleeding (see section 4.4).

Antidiabetics:

Data have shown that diclofenac, as in PANAMOR can be given together with oral antidiabetic medicines without influencing their clinical effect, however, there have been reports of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the

antidiabetic medicines during treatment with diclofenac, as in PANAMOR. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

Methotrexate:

Diclofenac, as in PANAMOR, can inhibit the tubular renal clearance of methotrexate thereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, as in PANAMOR, are administered less than 24 hours before or after treatment with methotrexate, since blood concentrations of methotrexate may rise, and the toxicity of this medicine be increased. Weekly blood count monitoring during the first few weeks of the combination is recommended. Monitoring should be increased in patients with impaired kidney function or in the elderly.

Pemetrexed in patients with normal renal function, CrCl > 80 ml/min:

Increased risk of pemetrexed toxicity due to decrease in pemetrexed clearance. Biological monitoring of renal function is recommended.

Calcineurin inhibitors (e.g. Ciclosporin, tacrolimus):

Nephrotoxicity of calcineurin inhibitors may be enhanced by NSAIDs, such as PANAMOR, via renal prostaglandin mediated effects. During combined treatment, monitoring of renal function is recommended, especially in the elderly.

Deferasirox:

The concomitant administration of NSAIDs, such as PANAMOR and deferasirox may increase the risk of gastrointestinal toxicity. Close clinical monitoring should be performed when these medicines are combined.

Quinolone antibacterials:

Convulsions may occur due to an interaction between quinolones and NSAIDs, such as diclofenac, as in PANAMOR. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving PANAMOR.

Phenytoin:

When using phenytoin concomitantly with diclofenac, as in PANAMOR, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.

Colestipol and cholestyramine:

These medicines can induce a delay or decrease in absorption of diclofenac, as in PANAMOR. Therefore, it is recommended to administer PANAMOR at least one hour before or 4 to 6 hours after administration of colestipol/ cholestyramine.

Potent CYP2C9 inhibitors:

Caution is recommended when co-prescribing diclofenac, as in PANAMOR with potent CYP2C9 inhibitors (such as sulfinpyrazone and voriconazole), which could result in a significant increase in peak plasma concentration and exposure to diclofenac due to inhibition of diclofenac, as in PANAMOR, metabolism.

Mifepristone:

PANAMOR should not be used for 8 to 12 days after mifepristone administration as PANAMOR can reduce the effect of mifepristone.

General

Acute allergic reactions have been reported. Because of the possibility of cross sensitivity due to structural relationships that 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.

Plasma concentrations are significantly decreased by the concomitant administration of therapeutic doses of aspirin.

PANAMOR may increase the half-life of probenecid.

Use with care together with other protein-bound medicines e.g. tolbutamide, coumarin and hydantoin.

4.6 Fertility, pregnancy and lactation

PANAMOR should not be given to pregnant woman or lactating women (see section 4.3 and 4.4).

Pregnancy

It is recommended that PANAMOR is avoided in pregnant women at 20 weeks or later in pregnancy (see section 4.3 and 4.6).

Avoid prescribing NSAIDs, such as diclofenac as in PANAMOR, at 30 weeks and later in pregnancy because of the additional risk of premature closure of the foetal ductus arteriosus (see section 4.3 and 4.6).

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation wis increased from less than 1 %, up to approximately 1,5 %.

The risk is believed to increase with dose and duration of therapy.

In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, diclofenac, as in PANAMOR, should not be given unless clearly necessary. If diclofenac , as in PANAMOR is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible (see section 4.4).

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension).
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Breastfeeding

Diclofenac, as in PANAMOR passes into the breast milk in small amounts. Therefore, PANAMOR should not be administered during breast feeding in order to avoid undesirable effects in the infant (see section 4.3).

Fertility

The use of PANAMOR 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 PANAMOR should be considered (see section 4.4).

4.7 Effects on ability to drive and use machines

Since adverse reactions such as dizziness, vertigo, somnolence ,blurred vision and other ocular reactions have been reported in patients receiving PANAMOR, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that PANAMOR does not adversely affect their ability to do so (see section 4.8).

4.8 Undesirable effects

a) Summary of the safety profile

The most commonly observed adverse events are gastrointestinal in nature or injection site reactions which are generally mild and transitory.

Data suggest that the use of diclofenac injectable solution, such as PANAMOR-75 mg INJECTION, is associated with injection site reactions, such as pain and haematoma.

After administering diclofenac, as in PANAMOR the following have also been reported: nausea, vomiting, diarrhoea and constipation.

The known adverse reactions with PANAMOR when used intramuscularly were injection site reactions, often related to an administration procedure, including pain at the injection site, erythema and rash. In some cases, hypersensitivity reactions also with generalised symptoms have been reported after treatment.

Administration of PANAMOR SUPPOSITORIES may give rise to systemic undesirable effects as they may cause exacerbation of haemorrhoids.

b) Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Infections and infestations		Injection site abscess	
Blood and the lymphatic system disorders		Thrombocytopenia, leucopoenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis	
Immune system disorders		Hypersensitivity reactions, anaphylactic and anaphylactoid reactions (including	

		hypotension and shock), angioneurotic oedema (including facial oedema)	
Psychiatric disorders		Disorientation depression, insomnia, nightmare, irritability, psychotic disorder	Agitation.
Nervous system disorders	Vertigo, headache, dizziness.	Somnolence, tiredness, disturbances of sensation, paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident	Drowsiness, nervousness. confusion, hallucinations, malaise
Eye disorders		Visual disturbance, blurred vision, diplopia	ocular reactions optic neuritis
Ear and labyrinth disorders		Tinnitus, hearing disorders.	
Cardiac disorders		Palpitations, chest pain, cardiac failure, myocardial infarction	Oedema,
Vascular disorders		Hypertension, vasculitis	
Respiratory, thoracic and mediastinal disorders		Asthma (including dyspnoea), pneumonitis, bronchospasm	
Gastrointestinal disorders	Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, nausea, vomiting, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, gastritis, diarrhoea, anorexia	Haemorrhagic diarrhoea, gastrointestinal ulcer (with or without bleeding or perforation, colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease)), stomatitis, glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis	Ischaemic colitis
Hepatobiliary disorders	Transaminases increased (SGOT, SGPT)	Hepatitis, jaundice**,** liver disorder, fulminant hepatitis, increase in hepatic enzymes, hepatic necrosis, hepatic failure	Abnormalities of liver function tests.
Skin and subcutaneous tissue disorders	Rash	Urticaria, eczema, erythema, erythema multiforme, bullous reactions, including Stevens-Johnson syndrome and toxic	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

		epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus	
Musculoskeletal and connective tissue disorders	Limb discomfort		
Renal and urinary disorders		Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis	Renal function impairment
Reproductive system and breast disorders		Impotence	
General disorders and administrative site conditions	Injection site reactions, injection site pain, injection site induration**,** application site irritation (suppositories),	Injection site necrosis	Nicolau syndrome.

c) Description of selected adverse reactions

Allergic reactions which include angio-oedema, bronchospasm, urticaria and anaphylactic reactions have occurred.

Data consistently point towards an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, as in PANAMOR, particularly at high doses (150 mg daily) (see section 4.3 and 4.4).

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. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088/ +27 (0)11 239-6200

4.9. Overdose

Symptoms

There is no typical clinical picture resulting from PANAMOR overdosage. Overdosage can cause symptoms such as vomiting, epigastric pain, gastrointestinal haemorrhage, diarrhoea, dizziness, disorientation, excitation, coma, drowsiness, tinnitus fainting or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible.

Treatment

Management of acute poisoning with PANAMOR essentially consists of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.

Special measures such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating PANAMOR due to the high protein binding and extensive metabolism. Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patient's clinical condition.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 3.1 Anti-rheumatics (anti-inflammatory agents)

Pharmacotherapeutic group: Non-steroidal anti-inflammatory drugs (NSAIDs):

ATC code: M01AB05

Mechanism of action

Diclofenac sodium is a non-steroidal anti-inflammatory compound with analgesic, anti-inflammatory, antirheumatic and antipyretic properties.

In vitro, its active medicine strongly inhibits prostaglandin-synthetase and also has an inhibitory effect on platelet aggregation.

Inhibition of prostaglandin biosynthesis, which has been demonstrated experimentally, is regarded as having an important bearing on its mechanism of action. Prostaglandins play a major role in the causation of inflammation, pain and fever.

Diclofenac, administered intramuscularly, exert an analgesic effect within 30 minutes in moderately and severely painful states of non-rheumatic origin.

5.2 Pharmacokinetic properties

Distribution

Plasma concentrations show a linear relationship to the size of the dose. Peak levels are attained in the case of the suppositories, in less than 1 hour.

PANAMOR -75 SR TABLETS and PANAMOR 100 SR TABLETS:

The peak-plasma concentration of PANAMOR - 75 SR TABLETS and PANAMOR - 100 SR TABLETS is maintained over a longer period due to the larger quantity of diclofenac.

PANAMOR-75 INJECTION:

Peak plasma concentrations are attained 10 to 22 minutes after an intramuscular dose of PANAMOR-75 INJECTION.

Protein binding:

99,7 %.

Biotransformation

Diclofenac is subject to first-pass metabolism.

Elimination

Diclofenac sodium is eliminated principally by metabolism and subsequent urinary and biliary excretion of glucuronide and sulphate conjugates of the metabolites. The principal metabolite in man is the 4-hydroxy derivative of diclofenac sodium. The amount excreted in the urine accounts for 20 to 30 % of the dose, and that in bile for 10 to 20 %. The mean terminal elimination half-life of unchanged diclofenac is 1 to 2 hours.

Approximately 60 % of the dose administered is excreted via the kidneys in the form of metabolites, and less than 1 % in unchanged form. About 30 % of the dose is excreted in metabolised form in the faeces.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

PANAMOR-75 INJECTION: Benzyl alcohol, distilled water for injection, mannitol, propylene glycol, sodium hydroxide 20 % solution (for pH adjustment), sodium metabisulphite.

PANAMOR SUPPOSITORIES-12,5: Suppocire AM

PANAMOR SUPPOSITORIES-25: Suppocire AM

PANAMOR SUPPOSITORIES: Suppocire AM

PANAMOR - 75 SR TABLETS: Diethyl phthalate, ethylcellulose, ferric oxide red (C.I. 77491), ferric oxide yellow (C.I. 77492), hypromellose, magnesium stearate, macrogol 4000, povidone, stearic acid, talc, titanium dioxide (C. I. 77891)

PANAMOR - 100 SR TABLETS: Diethyl phthalate, ethylcellulose, ferric oxide red (C.I. 77491), ferric oxide yellow (C.I. 77492), hypromellose, magnesium stearate, macrogol 4000, povidone, stearic acid, talc, titanium dioxide (C. I. 77891)

6.2. Incompatibilities

PANAMOR-75 INJECTION: This medicine must not be mixed with other medicines except those mentioned in section 6.6.

PANAMOR - 75 SR TABLETS, PANAMOR - 100 SR TABLETS, PANAMOR SUPPOSITORIES-12,5, PANAMOR SUPPOSITORIES-25, PANAMOR SUPPOSITORIES: Not applicable

6.3 Shelf life

PANAMOR - 100 SR TABLETS	36 months
PANAMOR - 75 SR TABLETS	36 months
PANAMOR SUPPOSITORIES-25	24 months
PANAMOR SUPPOSITORIES-12,5	24 months
PANAMOR SUPPOSITORIES 100 mg	36 months
PANAMOR-75 INJECTION	36 months

6.4 Special precautions for storage

PANAMOR - 75 SR TABLETS and PANAMOR - 100 SR TABLETS:

Store at or below 25 °C.

Protect from light.

Keep in original packaging until required for use.

PANAMOR-75 INJECTION:

Store at or below 25 °C.

Protect ampoules from heat and light.

Keep in original packaging until required for use.

PANAMOR SUPPOSITORIES-12,5; PANAMOR SUPPOSITORIES-25; PANAMOR SUPPOSITORIES:

Store at or below 25 °C.

Protect from moisture.

Keep in original packaging until required for use.

6.5 Nature and contents of container

PANAMOR - 75 SR TABLETS:

30 tablets are packed in a clear polyvinylchloride blister strip sealed with an aluminium foil backing. One or more blister strips are packed into an outer cardboard carton together with a leaflet.

PANAMOR - 100 SR TABLETS:

28 tablets are packed in a clear polyvinylchloride blister strip sealed with an aluminium foil backing. One or more blister strips are packed into an outer cardboard carton together with a leaflet.

PANAMOR-75 INJECTION:

5 x 3 ml or 50 x 3 ml amber glass ampoules are packed in a polystyrene container with a leaflet.

PANAMOR SUPPOSITORIES-12,5:

5 suppositories packed in white opaque polyvinylchloride laminated to polyethylene. One or more strips are packed into an outer cardboard carton together with a leaflet.

PANAMOR SUPPOSITORIES-25:

5 suppositories packed in white opaque polyvinylchloride laminated to polyethylene. One or more strips are packed into an outer cardboard carton together with a leaflet.

PANAMOR SUPPOSITORIES:

5 suppositories packed in white opaque polyvinylchloride laminated to polyethylene. One or more strips are packed into an outer cardboard carton together with a leaflet.

Not all pack sizes are necessarily marketed.

6.6 Special precautions for disposal and other handling

To prepare an intravenous infusion, one PANAMOR -75 INJECTION should be diluted with 100 to 500 ml of either sodium chloride solution (0,9 %) or glucose solution (5 %). Both solutions should first be buffered with bicarbonate solution (0,5 ml 8,4 % or 1 ml 4,2 %). Only clear infusion solutions should be used. PANAMOR infusions should be freshly made up and used immediately. Once prepared, the infusion should not be stored (see section 4.2).

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBERS

PANAMOR-75 INJECTION:	W/3.1/52
PANAMOR SUPPOSITORIES-12,5:	27/3.1/0121
PANAMOR SUPPOSITORIES-25:	Z/3.1/172
PANAMOR SUPPOSITORIES:	Y/3.1/395
PANAMOR - 75 SR TABLETS:	29/3.1/0121
PANAMOR - 100 SR TABLETS:	29/3.1/0122

9. DATE OF FIRST AUTHORISATION

Date of registration:

PANAMOR - 75 SR TABLETS:	13 September 1996
PANAMOR - 100 SR TABLETS:	13 September 1996
PANAMOR-75 INJECTION:	15 March 1989
PANAMOR SUPPOSITORIES-12,5:	19 February 1993
PANAMOR SUPPOSITORIES-25:	24 August 1992
PANAMOR SUPPOSITORIES:	13 March 1992

10. DATE OF REVISION OF TEXT

27 January 2023

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

Botswana:	S2
PANAMOR - 75 SR TABLETS	B9322615
PANAMOR-75 INJECTION	B9302600

Namibia:	NS2
PANAMOR - 75 SR TABLETS	04/3.1/0438
PANAMOR - 100 SR TABLETS	04/3.1/0216
PANAMOR-75 INJECTION	04/3.1/0098
PANAMOR SUPPOSITORIES-12,5	04/3.1/0101
PANAMOR SUPPOSITORIES-25	04/3.1/0450
PANAMOR SUPPOSITORIES	04/3.1/0099

Zimbabwe:	P.P.
PANAMOR-75 INJECTION	91/3.1/2477

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