Approved Professional Information for NATPEM

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

NATPEM 100 mg concentrate for solution for infusion

NATPEM 500 mg concentrate for solution for infusion

NATPEM 1000 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NATPEM 100: Each 4 mL vial of NATPEM contains 100 mg pemetrexed.

NATPEM 500: Each 20 mL vial of NATPEM contains 500 mg pemetrexed.

NATPEM 1000: Each 40 mL vial of NATPEM contains 1 000 mg pemetrexed.

Each vial contains 25 mg/mL pemetrexed.

Sugar free.

For the full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless to slightly yellow to brown, brown-yellow or green-yellow solution, free from particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NATPEM is indicated for the treatment of patients with malignant pleural mesothelioma in combination with cisplatin.

NATPEM is indicated in combination with cisplatin therapy for the initial treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.

NATPEM is indicated as monotherapy for the treatment of patients with locally advanced or metastatic adenocarcinoma of the lung after prior chemotherapy.

NATPEM is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic adenocarcinoma of the lung in patients whose disease has not progressed immediately following standard chemotherapy.

4.2 Posology and method of administration

Posology:

NATPEM should only be administered under the supervision of a medical practitioner qualified in the use of anti-cancer chemotherapy.

Malignant pleural mesothelioma:

Combination use with cisplatin:

Adults: In patients treated for malignant pleural mesothelioma, the recommended dose of NATPEM is 500 mg/m^2 administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle. The recommended dose of cisplatin is 75 mg/m^2 infused over 2 hours approximately 30 minutes after completion of NATPEM infusion on the first

day of each 21-day cycle.

Patients should receive appropriate hydration prior to and/or after receiving

cisplatin.

Adenocarcinoma of the lung:

Single medicine use:

Adults: In patients treated for adenocarcinoma of the lung, the

recommended dose of NATPEM is 500 mg/m^2 administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

Combination use with cisplatin:

Adults: In patients treated for non-small cell lung cancer: the recommended dose of NATPEM is 500 mg/m^2 administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

The recommended dose of cisplatin is 75 mg/m^2 infused over 2 hours approximately 30 minutes after completion of the NATPEM infusion on the first day of each 21-day cycle. Patients should receive appropriate hydration prior to and/or after receiving cisplatin.

Premedication regimen:

To reduce the incidence and severity of skin reactions, a corticosteroid

should be given the day prior to, on the day of, and the day after NATPEM

administration. The corticosteroid should be equivalent to 4 mg of

dexamethasone administered orally twice a day (see section 4.4).

To reduce toxicity, patients treated with NATPEM should also receive vitamin supplementation (see section 4.4). Patients must take oral folic acid or multivitamin containing folic acid (350 to 1000 mcg) on a daily basis. At least 5 daily doses of folic acid must be taken during the 7 days preceding the first dose of NATPEM, and dosing should

continue during the full course of therapy and for 21 days after the last dose of NATPEM. Patients must also receive an intramuscular injection of vitamin B_{12} (1000 mcg) in the week preceding the first dose of NATPEM and every 3 cycles thereafter.

Monitoring:

Patients receiving NATPEM should be monitored before each dose with a full blood count, including a differential and platelet count. Periodic blood chemistry tests should be collected to evaluate renal and hepatic function. Absolute neutrophil count (ANC) should be ≥ 1500 cells/mm^3 and platelets should be ≥ 100 000 cells/mm^3 prior to the start of each cycle.

Dose adjustments:

Dose adjustments at the start of a subsequent cycle should be based on nadir haematologic counts or maximum non-haematologic toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery, patients may be retreated using the guidelines in Tables 1, 2 and 3, which are applicable for NATPEM used as a

single medicine or in combination with cisplatin.

Table 1: Dose modification table for NATPEM (as single medicine or in combination) and cisplatin: haematological toxicities	
Nadir ANC < 500/mm^3 and nadir platelets ≥ 50 000/mm^3	75 % of previous dose (both NATPEM and cisplatin)
Nadir platelets ≤ 50 000/mm^3 regardless of nadir ANC	50 % of previous dose (both NATPEM and cisplatin)
Nadir platelets ≤ 50 000/mm^3 with bleeding[a], regardless of nadir ANC	50 % of previous dose (both NATPEM and cisplatin)
[a] These criteria meet the National Cancer Institute Common Toxicity Criteria (CTC v2.0; NCI 1998) definition of ≥ CTC Grade 2 bleeding.	

If patients develop non-haematological toxicities (excluding

neurotoxicity) ≥ Grade 3, treatment should be withheld until resolution to less than or equal to the patient's pre-therapy value. Treatment should be resumed according to the guidelines in Table 2.

Table 2: Dose modification table for NATPEM (as single medicine or in combination) and cisplatin: non-haematological toxicities [a, b]		
	Dose of NATPEM (mg/m^2)	**Dose of cisplatin (mg/m^2)**
Any Grade 3 or 4 toxicities except mucositis	75 % of previous dose	75 % of previous dose
Any diarrhoea requiring hospitalisation (irrespective of grade) or Grade 3 or 4 diarrhoea	75 % of previous dose	75 % of previous dose
Grade 3 or 4 mucositis	50 % of previous dose	100 % of previous dose
[a] National Cancer Institute Common Toxicity Criteria [b] Excluding neurotoxicity		

In the event of neurotoxicity, the recommended dose adjustment for NATPEM and cisplatin is documented in Table 3. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is observed.

Table 3: Dose modification table for NATPEM (as single medicine or in combination) and cisplatin: neurotoxicity		
CTC * Grade	**Dose of NATPEM (mg/m^2)**	**Dose of cisplatin (mg/m^2)**
0 – 1	100 % of previous dose	100 % of previous dose
2	100 % of previous dose	50 % of previous dose
* Common Toxicity Criteria (CTC)		

Treatment with NATPEM should be discontinued if a patient experiences any haematologic or non-haematologic Grade 3 or 4 toxicity after two dose reductions or immediately if Grade 3 or 4 neurotoxicity is observed.

Elderly: There has been no indication that patients 65 years of age or older are at increased risk of adverse events compared to patients younger than 65 years old. No dose reductions other than those recommended for all patients are necessary.

Patients with renal impairment (standard Cockcroft and Gault formula or glomerular filtration rate measured by Tc99m-DPTA serum clearance method): Pemetrexed is primarily eliminated unchanged by renal excretion. Patients with creatinine clearance of ≥ 45 mL/min required no dosage adjustments other than those recommended to all patients. There are insufficient data on the use of NATPEM in patients with creatinine clearance below 45 mL/min; therefore, the use of NATPEM is not recommended (see section 4.4).

Patients with hepatic impairment: No relationships between aspartate aminotransferase (AST) / serum glutamic-oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT) / serum glutamic pyruvic transaminase (SGPT), or total bilirubin and NATPEM pharmacokinetics were identified. However, patients with hepatic impairment such as bilirubin > 1,5 times the upper limit of normal and/or transaminase > 3,0 times the upper limit of normal (hepatic metastases absent) or > 5,0 times the upper limit of normal (hepatic metastases present) have not been specifically studied.

Paediatrics: NATPEM is not recommended for use in patients under 18 years of age, as safety and efficacy have not been established in this group of patients.

Method of administration

For intravenous use.

4.3 Contraindications

- Hypersensitivity to pemetrexed or to any of the excipients listed in section 6.1.
- Concomitant yellow fever vaccine (see section 4.5).

4.4 Special warnings and precautions for use

NATPEM can suppress bone marrow function as manifested by neutropenia, thrombocytopenia and anaemia (or pancytopenia) (see section 4.8). Myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for myelosuppression during therapy and NATPEM should not be given to patients until absolute neutrophil count (ANC) returns to ≥ 1500 cells/mm^3 and platelet count returns to ≥ 100,000 cells/mm^3. Dose reductions for subsequent cycles are based on nadir ANC, platelet count and maximum non-haematologic toxicity seen from the previous cycle (see

section 4.2).

Less toxicity and reduction in Grade 3/4 haematologic and non-haematologic toxicities such as neutropenia, febrile neutropenia and infection with Grade 3/4 neutropenia were reported when pre-treatment with folic acid and vitamin B_{12} was administered. Therefore, all patients treated with NATPEM must be instructed to take folic acid and vitamin B_{12} as a prophylactic measure to reduce treatment-related toxicity (see section 4.2).

Skin reactions have been reported in patients not pre-treated with a corticosteroid. Pre-treatment with dexamethasone (or equivalent) can reduce the incidence and severity of skin reactions (see section 4.2).

An insufficient number of patients has been studied with creatinine clearance of below 45 mL/min. Therefore, the use of NATPEM in patients with creatinine clearance of < 45 mL/min is not recommended (See section 4.2).

Patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min) should avoid taking nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, and acetylsalicylic acid (> 1,3 g daily) for 2 days before, on the day of, and 2 days following NATPEM administration (see section 4.5).

In patients with mild to moderate renal insufficiency eligible for NATPEM therapy NSAIDs with long elimination half-lives should be interrupted for at least 5 days prior to, on the day of, and at least 2 days following NATPEM administration (see section 4.5).

Serious renal events, including acute renal failure, have been reported with PEMETREXED alone or in association with other chemotherapeutic medicines. Many of the patients in whom these occurred had underlying risk factors for the development of renal events including dehydration or pre-existing hypertension or diabetes. Nephrogenic diabetes insipidus and renal tubular necrosis were also reported in post marketing setting with PEMETREXED alone or with other chemotherapeutic medicines (see section 4.8). Most of these events resolved after PEMETREXED withdrawal. Patients should be regularly monitored for acute tubular necrosis, decreased renal function and signs and symptoms of nephrogenic diabetes insipidus (e.g. hypernatraemia).

The effect of third space fluid, such as pleural effusion or ascites, on pemetrexed is not fully defined, therefore drainage of third space fluid collection prior to NATPEM treatment should be considered but may not be necessary.

Due to the gastrointestinal toxicity of PEMETREXED given in combination with cisplatin, severe dehydration has been observed. Therefore, patients should receive adequate antiemetic treatment and appropriate hydration prior to and/or after receiving treatment.

Serious cardiovascular events, including myocardial infarction and cerebrovascular events have been uncommonly reported with PEMETREXED usually when given in combination with another cytotoxic medicine. Most of the patients in whom these events have been observed had pre-existing cardiovascular risk factors (see section 4.8). Immunosuppressed status is common in cancer patients. As a result, concomitant use of live attenuated vaccines is not recommended (see section 4.5).

NATPEM can have genetically damaging effects. Sexually mature males are advised not to father a child during the treatment and up to 6 months thereafter. Contraceptive measures or abstinence are recommended. Owing to the possibility of NATPEM treatment causing irreversible infertility, men are advised to seek counselling on sperm storage before starting treatment.

Women of childbearing potential must use effective contraception during treatment with NATPEM (see section 4.6).

Cases of radiation pneumonitis have been reported in patients treated with radiation either prior, during, or subsequent to their PEMETREXED therapy. Particular attention should be paid to these patients and caution exercised with use of other radio-sensitising medicines.

Cases of radiation recall have been reported in patients who received radiotherapy weeks or years previously.

4.5 Interaction with other medicines and other forms of interaction

NATPEM is mainly eliminated unchanged renally by tubular secretion and to a lesser extent by glomerular filtration.

Concomitant administration of nephrotoxic medicines (e.g. aminoglycoside, loop diuretics, platinum compounds, ciclosporin) could potentially result in delayed clearance of NATPEM. This combination should be used with caution. If necessary, creatinine clearance should be closely monitored.

Concomitant administration of substances that are also tubularly secreted (e.g. probenecid, penicillin) could potentially result in delayed clearance of NATPEM. Caution should be made when these medicines are combined with NATPEM. If necessary, creatinine clearance should be closely monitored.

In patients with normal renal function (creatinine clearance ≥ 80 mL/min), high doses of non-steroidal anti-inflammatory medicines (NSAIDs, such as ibuprofen > 1600 mg/day) and acetylsalicylic acid at higher dose (≥ 1,3 g daily) may decrease NATPEM elimination and, consequently, increase the occurrence of NATPEM adverse reactions. Therefore, caution should be made when administering higher doses of NSAIDs or acetylsalicylic acid, concurrently with NATPEM to patients with normal function (creatinine clearance ≥ 80 mL/min).

In patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min), the concomitant administration of NATPEM with NSAIDs (e.g. ibuprofen) or acetylsalicylic acid at higher dose should be avoided for 2 days before, on the day of, and 2 days following NATPEM administration (see section 4.4).

In the absence of data regarding potential interaction with NSAIDs having longer half-lives such as piroxicam or rofecoxib, the concomitant administration with NATPEM in patients with mild to moderate renal insufficiency should be interrupted for at least 5 days prior to, on the day of, and at least 2 days following NATPEM administration (see section 4.4). If

concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression and gastrointestinal toxicity.

Aspirin administered in low to moderate doses (325 mg orally every 6 hours) does not affect the pharmacokinetics of NATPEM.

The pharmacokinetics of NATPEM are not influenced by concurrently administered cisplatin or carboplatin. Similarly, the pharmacokinetics of total platinum are unaltered by NATPEM.

Oral folic acid and intramuscular vitamin B_{12} supplementation do not affect the pharmacokinetics of NATPEM.

NATPEM undergoes limited hepatic metabolism. Results from *in vitro* studies with human liver microsomes indicated that NATPEM would not be predicted to cause clinically significant inhibition of the metabolic clearance of medicines metabolised by CYP3A, CYP2D6, CYP2C9, and CYP1A2.

Interactions common to all cytotoxics

Due to the increased thrombotic risk in patients with cancer, the use of anticoagulation treatment is frequent. The high intra-individual variability of the coagulation status during diseases and the possibility of interaction between oral anticoagulants and anticancer chemotherapy require increased frequency of INR (international normalised ratio) monitoring, if it is decided to treat the patient with oral anticoagulants.

Concomitant use with yellow fever vaccine is contraindicated as there is a risk of fatal generalised vaccinate disease (see section 4.3).

Concomitant use of live attenuated vaccines is not recommended (except yellow fever, for which concomitant use is contraindicated) as there is a risk of systemic, possibly fatal, disease. The risk is increased in patients who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where it exists (poliomyelitis) (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in males and females

Women of childbearing potential must use effective contraception during treatment with NATPEM.

NATPEM can have genetically damaging effects. Sexually mature males are advised not to father a child during the treatment and up to 6 months thereafter. Contraceptive measures or abstinence are recommended.

Pregnancy

There is no data on the use of NATPEM in pregnant women but NATPEM, like other anti-metabolites, is suspected to cause serious birth defects when administered during pregnancy. Animal studies have shown reproductive toxicity. NATPEM should not be used during pregnancy due to the potential hazard to the foetus. Women should also be advised to avoid becoming pregnant while being treated with NATPEM.

Breastfeeding

It is not known whether NATPEM is excreted in human milk and adverse reactions on the breastfeeding child cannot be excluded. Breastfeeding must be discontinued during NATPEM therapy.

Fertility

Owing to the possibility of NATPEM treatment causing irreversible infertility, men are advised to seek counselling on sperm storage before starting NATPEM treatment.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, it has been reported that NATPEM may cause fatigue. Therefore, patients should be cautioned against driving a vehicle or operating machines if this event occurs

4.8 Undesirable effects

Infections and infestations:

Frequent: infection[a], pharyngitis, sepsis[b]

Less frequent: dermo-hypodermitis

Blood and the lymphatic system disorders:

Frequent: neutropenia, leukopenia, decreased haemoglobin, febrile neutropenia, decreased platelet count

Less frequent: pancytopenia, autoimmune haemolytic anaemia

Immune system disorders:

Frequent: hypersensitivity

Less frequent: anaphylactic shock

Metabolism and nutrition disorders:

Frequent: dehydration

Nervous system disorders:

Frequent: taste disorder, peripheral motor neuropathy, sensory neuropathy, dizziness

Less frequent: cerebrovascular accident, ischaemic stroke, intracranial haemorrhage

Eye disorders:

Frequent: conjunctivitis, dry eye, increased lacrimation, keratoconjunctivitis sicca, eyelid oedema, ocular surface disease

Cardiac disorders:

Frequent: cardiac failure, dysrhythmia

Less frequent: angina, myocardial infarction, coronary artery disease, supraventricular dysrhythmia

Vascular disorders:

Less frequent: peripheral ischaemia[c]

Respiratory, thoracic and mediastinal disorders:

Less frequent: pulmonary embolism, interstitial pneumonitis[bd]

Gastrointestinal disorders:

Frequent: stomatitis, anorexia, vomiting, diarrhoea, nausea, dyspepsia, constipation, abdominal pain, mucositis

Less frequent: rectal haemorrhage, gastrointestinal haemorrhage, intestinal perforation, oesophagitis, colitis[e]

Hepatobiliary disorders:

Frequent: increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST)

Less frequent: hepatitis

Skin and subcutaneous tissue disorders:

Frequent: rash, skin exfoliation, hyperpigmentation, pruritus, erythema multiforme, alopecia, urticaria, desquamation

Less frequent: erythema, Stevens-Johnson syndrome[b], toxic epidermal necrolysis[b], pemphigoid, bullous dermatitis, acquired epidermolysis bullosa,

erythematous oedema[f], pseudocellulitis, dermatitis, eczema, prurigo

Renal and urinary disorders:

Frequent: decreased creatine clearance, increased blood creatinine[e], renal failure,

decreased glomerular filtration rate

Frequency not known: nephrogenic diabetes insipidus, renal tubular necrosis

General disorders and administration site conditions:

Frequent: fatigue, pyrexia, pain, oedema, chest pain, mucosal inflammation

Investigations:

Frequent: increased gamma-glutamyltransferase

Injury, poisoning and procedural complications:

Less frequent: radiation oesophagitis, radiation pneumonitis, radiation recall phenomenon.

[a] with and without neutropenia

[b] in some cases fatal

[c] sometimes leading to extremity necrosis

[d] with respiratory insufficiency

[e] seen only in combination with cisplatin

[f] mainly of the lower limbs

Reporting of suspected adverse reactions:

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

Reported symptoms of overdose include neutropenia, anaemia, thrombocytopenia, mucositis, sensory polyneuropathy and rash. Anticipated complications of overdose include bone marrow suppression as manifested by neutropenia, thrombocytopenia and anaemia. In addition, infection with or without fever, diarrhoea, and/or mucositis may be seen. In the event of suspected overdose, patients should be monitored with blood counts and should receive supportive therapy as necessary. The use of leucovorin in the management of NATPEM overdose should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 Cytostatic agents.

Pharmacotherapeutic group: Folic acid analogues.

ATC code: L01BA04

Pemetrexed is a multi-targeted anti-cancer antifolate medicine that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication.

In vitro studies have shown that pemetrexed behaves as a multitargeted antifolate by inhibiting thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are key folate-dependent enzymes for the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is transported into cells by both the reduced folate carrier and membrane folate binding protein transport systems.

Once in the cell, pemetrexed is rapidly and efficiently converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are even more potent inhibitors of TS and GARFT. Polyglutamation is a time- and concentration- dependent process that occurs in tumour cells and, to a lesser extent, in normal tissues.

Polyglutamated metabolites have an increased intracellular half-life resulting in prolonged medicine action in malignant cells.

5.2 Pharmacokinetic properties

Pemetrexed has a steady-state volume of distribution of 16,1 L/m^2. *In vitro* studies indicate that pemetrexed is approximately 81 % bound to plasma proteins. Binding was not notably affected by varying degrees of renal impairment. Pemetrexed undergoes limited hepatic metabolism.

Pemetrexed is primarily eliminated in the urine, with 70 % to 90 % of the administered dose being recovered unchanged in urine within the first 24 hours following administration. *In vitro* studies indicate that pemetrexed is actively secreted by OAT3 (organic anion transporter). Pemetrexed total systemic clearance is 91,8 mL/min and the elimination half-life from plasma is 3,5 hours in patients with normal renal function (creatinine clearance of 90 mL/min). Between patient variability in clearance is moderate at 19,3 %. Pemetrexed total systemic exposure (AUC) and maximum plasma

concentration increase proportionally with dose. The pharmacokinetics of

pemetrexed are consistent over multiple treatment cycles.

The pharmacokinetic properties of pemetrexed are not influenced by concurrently administered cisplatin. Oral folic acid and intramuscular vitamin B_{12} supplementation do not affect the pharmacokinetics of pemetrexed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid (E330)

L-arginine (pH adjuster)

L-cysteine

Propylene glycol.

6.2 Incompatibilities

NATPEM is physically incompatible with diluents containing calcium, including lactated Ringer's injection and Ringer's injection.

Co-administration of NATPEM with other medicines and diluents has not been studied and therefore is not recommended.

NATPEM contains l-arginine as an excipient (see section 6.1). L-arginine is incompatible with cisplatin resulting in degradation of cisplatin. NATPEM must not be mixed with cisplatin. If NATPEM is given as combination therapy with cisplatin, cisplatin should be infused approximately 30 minutes after

completion of NATPEM infusion.

Intravenous lines should be flushed after administration of NATPEM.

6.3 Shelf life

Unopened:

2 years.

Store at or below 25 °C.

After opening:

When prepared as directed, infusion solutions of NATPEM contain no preservatives. Chemical and physical in-use stability of the infusion solution were demonstrated for 24 hours at refrigerated temperature (2 °C – 8 °C). From a microbiological point of view, NATPEM should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not be longer than 24 hours at 2 °C – 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Keep the vial in the outer carton until required for use.

For storage conditions after dilution of NATPEM, see section 6.3.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

7 mL / 20 mL / 50 mL type I, clear, colourless glass vial, sealed with a round bromobutyl rubber stopper, an aluminium cap and a blue flip-top, packed in an outer carton.

Pack size: one vial.

6.6 Special precautions for disposal and other handling

The NATPEM solution must be prepared as follows:

1. Use appropriate aseptic technique during the dilution of NATPEM for intravenous infusion administration.
2. Calculate the dose and the number of NATPEM vials needed. Each vial contains an excess of NATPEM to facilitate delivery of the label amount.
3. The appropriate volume of NATPEM solution must only be diluted to 100 mL with 0,9 % *m/v* sodium chloride (saline) infusion solution, without preservative or 5 % *m/v* glucose (dextrose) infusion solution, without preservative.
4. NATPEM solutions prepared as directed above are compatible with polyvinyl chloride and polyolefin lined administration sets and infusion bags.
5. Infusion solutions of NATPEM contain no preservatives. Chemical and physical in-use stability of the infusion solution was demonstrated for 24 hours at refrigerated temperature (2 °C – 8 °C). From a microbiological point of view, NATPEM should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not be longer than 24 hours at 2 °C – 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.
6. NATPEM must be inspected visually for particulate matter and discolouration prior to administration.
7. NATPEM solution should then be administered as an intravenous infusion over 10 minutes.
8. Procedures for proper handling and disposal should be observed. Care should be exercised in the handling and preparation of infusion solutions of NATPEM. Any unused contents of the vial should be discarded.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand 1685

South Africa

8. REGISTRATION NUMBERS

NATPEM 100: 56/26/0053

NATPEM 500: 56/26/0054

NATPEM 1000: 56/26/0055

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 June 2023

10. DATE OF REVISION OF THE TEXT