PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

PEXALI® 100, powder for concentrate for solution for infusion

PEXALI® 500, powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 ml vial contains 100 mg pemetrexed and each 50 ml vial contains 500 mg pemetrexed, as pemetrexed disodium 2,5 hydrate.

After reconstitution (see section 6.6), each vial contains 25 mg/ml of pemetrexed.

Excipients with known effect:

PEXALI contains:

- about 11 mg sodium per 100 mg vial (essentially 'sodium-free')
- approximately 54 mg of sodium per 500 mg vial.

Contains sugar (mannitol):

- PEXALI 100 contains 106,4 mg mannitol per vial and PEXALI 500 contains 500 mg mannitol per vial.

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to faint yellow lyophilised cake or powder.

The reconstituted solution is a clear, colourless solution without visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

PEXALI is indicated as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

4.2 Posology and method of administration

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

Posology

Malignant pleural mesothelioma:

Combination use with cisplatin:

Adults: In patients treated for malignant pleural mesothelioma, the recommended dose of PEXALI 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 PEXALI infusion on the first day of each 21-day cycle.

Patients should receive appropriate hydration prior to and/or after receiving cisplatin. See cisplatin professional information for specific dosing advice.

Non-small cell lung cancer:

Single medicine use:

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

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 PEXALI 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 PEXALI should also receive vitamin supplementation (see section 4.4). Patients should take oral folic acid or a multivitamin containing folic acid (350 to 1 000 µg) on a daily basis. At least five doses of folic acid must be taken during the seven days preceding the first dose of PEXALI. Dosing must continue during the full course of therapy and for 21 days after the last dose of PEXALI. Patients should also receive an intramuscular injection of vitamin B_{12} (1 000 µg) in the week preceding the first dose of PEXALI and once every three cycles thereafter.

Monitoring:

Patients receiving PEXALI should be monitored before each dose with a full blood count, including a differential white cell count (WCC) and platelet count. Periodic blood chemistry tests should be done to evaluate renal and hepatic function. The absolute neutrophil count (ANC) should be ≥ 1 500 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 enough time for recovery. Upon recovery, patients should be retreated using the guidelines in Tables 1, 2, and 3, which are applicable for PEXALI used as monotherapy or in combination with cisplatin.

Table 1: Dose modification table for PEXALI (monotherapy or in combination) and cisplatin - haematologic toxicities

Nadir ANC < 500/mm^3 and nadir platelets ≥ 50 000/mm^3	75 % of previous dose (both PEXALI and cisplatin)
Nadir platelets ≤ 50 000/mm^3 without bleeding regardless of nadir ANC	50 % of previous dose (both PEXALI and cisplatin)
Nadir platelets ≤ 50 000/mm^3 with bleeding[a] regardless of nadir ANC	50 % of previous dose (both PEXALI and cisplatin)

[a] These criteria meet the National Cancer Institute, Common Toxicity Criteria version 2.0 (NCI 1998) definition of ≥ CTC Grade 2 bleeding.

If patients develop non-haematologic toxicities ≥ Grade 3 (excluding neurotoxicity), PEXALI should be withheld until resolution to less than or equal to the patient's pre-treatment value. Treatment should be resumed according to the guidelines in Table 2.

Table 2: Dose modification table for PEXALI (as monotherapy or in combination) and cisplatin: non-haematologic toxicities [a, b]		
	Dose of PEXALI (mg/m^2)	**Dose for 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 (CTC) [b] Excluding neurotoxicity		

In the event of neurotoxicity, the recommended dose adjustment for PEXALI and cisplatin is documented in Table 3. Therapy should be discontinued in patients if Grade 3 or 4 neurotoxicity is observed.

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

Treatment with PEXALI should be discontinued if a patient experiences any haematologic or non-haematologic Grade 3 or 4 toxicity after two dose reductions

(except Grade 3 transaminase elevations) or immediately if Grade 3 or 4 neurotoxicity is observed.

Elderly:

There is 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.

Paediatric population:

PEXALI 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.

Patients with renal impairment:

(Standard Cockcroft and Gault formula or glomerular filtration rate measured Tc99m-DPTA serum clearance method): Pemetrexed is primarily eliminated unchanged by renal excretion. Patients with creatinine clearance of ≥ 45 ml/min require no dose adjustments other than those recommended for all patients. There are insufficient data on the use of pemetrexed as in PEXALI in patients with creatinine clearance below 45 ml/min; therefore, the use of PEXALI is not recommended (see section 4.4).

Patients with hepatic impairment:

No relationships between AST (SGOT), ALT (SGPT), or total bilirubin and pemetrexed 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.

Method of administration

PEXALI should be administered as an intravenous infusion over 10 minutes.

For precautions to be taken before handling or administering PEXALI, see section 6.6.

For instructions on reconstitution and dilution of PEXALI before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to pemetrexed or any of the excipients of PEXALI listed in section 6.1.
- Concomitant yellow fever vaccine.

4.4 Special warnings and precautions for use

PEXALI can suppress bone marrow function as manifested by neutropenia, thrombocytopenia, anaemia or pancytopenia (see section 4.8). Myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for myelosuppression during therapy and pemetrexed should not be given to patients until absolute neutrophil count (ANC) returns to ≥ 1 500 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 pemetrexed 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 have been studied with creatinine clearance of below 45 ml/min. Therefore, the use of PEXALI 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 non-steroidal 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 PEXALI administration (see section 4.5).

In patients with mild to moderate renal insufficiency eligible for pemetrexed 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 PEXALI administration (see section 4.5).

Serious renal events, including acute renal failure, have been reported with pemetrexed (contained in PEXALI) 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 with pemetrexed alone or with other chemotherapeutic medicines. 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 clinically significant third-space fluid collection prior to PEXALI treatment in patients with normal renal function 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 PEXALI.

Serious cardiovascular events, including myocardial infarction and cerebrovascular events have been 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).

Immunodepressed status is frequent in cancer patients. As a result, concomitant use of live attenuated vaccines is not recommended (see section 4.3 and 4.5).

Pemetrexed 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 PEXALI 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 PEXALI (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 radiosensitising substances.

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

Excipients with known effect

PEXALI 100 contains about 11 mg (less than 1 mmol) sodium per 100 mg vial and is essentially 'sodium-free'.

PEXALI 500 contains approximately 54 mg of sodium per 500 mg vial, equivalent to 2,7 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

The sodium content should be taken into account by patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction

Pemetrexed is mainly eliminated unchanged renally by tubular secretion and to a lesser extent by glomerular filtration. Concomitant administration of nephrotoxic medicines (such as aminoglycosides, loop diuretics, platinum compounds, ciclosporin) with PEXALI could potentially result in delayed clearance of pemetrexed. This combination should be used with caution. Creatinine clearance may need to be closely monitored if necessary.

Concomitant administration of substances that are also tubularly secreted (e.g., probenecid, penicillin) could potentially result in delayed clearance of pemetrexed.

Caution should be made when these medicines are combined with PEXALI. If necessary, creatinine clearance should be closely monitored.

In patients with normal renal function (creatinine clearance ≥ 80 ml/min), high doses of NSAIDs, such as ibuprofen > 1 600 mg/day) and aspirin at higher doses (≥ 1,3 g daily) may decrease pemetrexed elimination and, consequently, increase the occurrence of side effects. Therefore, caution should be made when administering higher doses of NSAIDs or aspirin, concurrently with PEXALI 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 PEXALI with NSAIDs (e.g., ibuprofen) or aspirin at higher doses should be avoided for at least 2 days before, on the day of, and at least 2 days following PEXALI 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 PEXALI 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 PEXALI administration (see section 4.4). If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression and gastrointestinal toxicity.

Acetylsalicylic acid administered in low to moderate doses (325 mg orally every 6 hours) does not affect the pharmacokinetics of pemetrexed as in PEXALI.

The pharmacokinetics of pemetrexed as in PEXALI are not influenced by concurrently administered cisplatin or carboplatin. Similarly, the pharmacokinetics of total platinum are unaltered by PEXALI. Oral folic acid and intramuscular vitamin B_{12} supplementation do not affect the pharmacokinetics of pemetrexed as in PEXALI.

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

Interactions common to all cytotoxic medicines:

Due to the increased thrombotic risk in patients with cancer, the use of anticoagulation treatment is common. The high intra-individual variability of the coagulation status during diseases and the possibility of interaction between oral anticoagulants and anti-cancer chemotherapy such as PEXALI require increased frequency of INR (International Normalised Ratio) monitoring, if it is decided to treat the patient with oral anticoagulants.

Yellow fever vaccine: Concomitant use is contraindicated: Risk of fatal generalised vaccination disease (see section 4.3).

Live attenuated vaccines (except yellow fever, for which concomitant use is contraindicated): Concomitant use is not recommended: 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

Pregnancy

Safety in pregnancy has not been established. Animal studies have shown reproductive toxicity such as birth defects and other defects on the development of the foetus, the course of gestation and peri- and post-development. PEXALI should be avoided during pregnancy due to the potential risk to the foetus. Women should also be advised to avoid becoming pregnant while being treated with PEXALI.

Contraception in males and females

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

Breastfeeding

Safety in lactation has not been established. It is not known whether pemetrexed is excreted in human milk. It is therefore recommended that breastfeeding is discontinued during PEXALI therapy.

Fertility

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

4.7 Effects on ability to drive and use machines

PEXALI may cause fatigue and dizziness. Therefore, patients should be cautioned against driving or operating machines or tools, if these events occur (see section 4.8).

4.8 Undesirable effects

Tabulated list of adverse reactions

TABLE 4

Frequencies of undesirable effects when pemetrexed as in PEXALI was used in combination with cisplatin, supplemented with folic acid and vitamin B_{12} in patients with malignant pleural mesothelioma:

System organ class	**Frequency**	**Event**

Infections and infestations	Frequent	Infection
Blood and lymphatic system disorders	Frequent	Decreased neutrophils/ granulocytes Decreased leukocytes Decreased haemoglobin Decreased platelets Febrile neutropenia
Metabolism and nutrition disorders	Frequent	Dehydration
Nervous system disorders	Frequent	Sensory neuropathy Dysgeusia
	Less frequent	Motor neuropathy
Eye disorders	Frequent	Conjunctivitis
Cardiac disorders	Less frequent	Dysrhythmia
Gastrointestinal disorders	Frequent	Nausea Vomiting Stomatitis/ Pharyngitis Anorexia Diarrhoea Constipation Dyspepsia
Hepatobiliary disorders	Frequent	Increased AST, ALT and GGT

Skin and subcutaneous tissue disorders	Frequent	Rash Alopecia Urticaria
Renal and urinary disorders	Frequent	Serum creatinine elevation Creatinine clearance decreased Renal failure
	Less frequent	Acute renal failure
	Frequency unknown	Nephrogenic diabetes insipidus and renal tubular necrosis
General disorders and administration site conditions	Frequent	Fatigue Pyrexia Chest pain
Injury, poisoning and procedural complications	Less frequent	Radiation recall (in patients who have previously received radiotherapy)

Single medicine pemetrexed after prior chemotherapy:

TABLE 5

Frequencies of undesirable effects when pemetrexed as in PEXALI was used as a single medicine supplemented with folic acid and vitamin B_{12} in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who received prior chemotherapy:

System organ class	**Frequency**	**Event**
Infections and infestations	Frequent	Infection without neutropenia, sepsis

Blood and lymphatic system disorders	Frequent	Decreased haemoglobin Decreased leukocytes Decreased neutrophils/ granulocytes Decreased platelets Febrile neutropenia
	Less frequently	Pancytopenia
Immune system disorders	Frequent	Allergic reaction/ hypersensitivity
	Less frequent	Immune-mediated haemolytic anaemia
	Frequency unknown	Anaphylactic shock
Nervous system disorders	Frequent	Motor neuropathy, sensory neuropathy
Cardiac disorders	Less frequent	Supraventricular dysrhythmias
Respiratory, thoracic and mediastinal disorders	Less frequent	Radiation pneumonitis, interstitial pneumonitis with respiratory insufficiency
Gastrointestinal disorders	Frequent	Nausea Anorexia Vomiting Stomatitis/ pharyngitis Diarrhoea Constipation Abdominal pain

	Less frequent	Colitis (including intestinal and rectal bleeding, sometimes fatal, intestinal perforation, intestinal necrosis and typhlitis) Oesophagitis/ radiation oesophagitis
Hepatobiliary disorders	Frequent	ALT (SGPT) elevation AST (SGOT) elevation
	Less frequent	Hepatitis
Skin and subcutaneous tissue disorders	Frequent	Rash/ desquamation Pruritus Alopecia Hyperpigmentation Erythema multiforme
	Less frequent	Bullous conditions including Stevens-Johnson syndrome and toxic epidermal necrolysis
	Frequency unknown	Erythematous oedema of the lower limbs, infectious and non-infectious disorders of the dermis, hypodermis and/or subcutaneous tissue (e.g. acute bacterial dermo-hypodermitis, pseudocellulitis, dermatitis)
Renal and urinary disorders	Frequent	Increased creatinine

	Less frequent	Acute renal failure
	Frequency unknown	Nephrogenic diabetes insipidus and renal tubular necrosis
General disorders and administration site conditions	Frequent	Fatigue Fever
	Less frequent	Oedema
Injury, poisoning and procedural complications	Less frequent	Radiation recall (in patients who have previously received radiotherapy)

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 via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: **https://www.sahpra.org.za**

4.9 Overdose

Symptoms

Neutropenia, anaemia, thrombocytopenia, mucositis, sensory neuropathy and rash have been reported.

Other complications may include bone marrow suppression, infection with or without fever, diarrhoea and mucositis.

Management

Patients should be monitored with blood counts and should receive supportive therapy as necessary. The use of leucovorin in the management of PEXALI overdosage should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category A 26 Cytostatic agents

Pemetrexed is a multi-targeted anti-cancer antifolate substance that acts by disrupting crucial folate-dependent metabolic processes essential for cell replication.

Pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyltransferase (GARFT), which are key folate-dependent enzymes for the biosynthesis of thymidine and purine nucleotides from the start. Pemetrexed is transported into cells by both the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are 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 action of the medicine in malignant cells.

5.2 Pharmacokinetic properties

Distribution

Pemetrexed has a steady-state volume of distribution of 16,1 ℓ and is approximately 81 % bound to plasma proteins. Binding is not notably affected by varying degrees of renal impairment.

Biotransformation

Pemetrexed undergoes limited hepatic metabolism.

Elimination

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.

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.

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

Mannitol, hydrochloric acid (to adjust pH), sodium hydroxide (to adjust pH).

6.2 Incompatibilities

PEXALI should only be reconstituted and diluted with 0,9 % sodium chloride injection, without preservative.

PEXALI is physically incompatible with solutions containing calcium, such as lactated Ringer's injection and Ringer's injection.

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

6.3 Shelf life

Unopened vial:

36 months at or below 25 °C.

Reconstituted and infusion solutions:

When prepared as directed, reconstituted and infusion solutions of PEXALI contain no antimicrobial preservatives. From a microbiological point of view, the product should therefore be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Chemical and physical stability of the reconstituted and infusion solution of PEXALI in 0,9 % sodium chloride injection were demonstrated for up to 24 hours after reconstitution of the original vial when refrigerated between 2 to 8 °C and at or below 25 °C.

6.4 Special precautions for storage

Unopened vials

Store the vial in the original container, at or below 25 °C. Do not freeze.

Storage of the reconstituted product in vials

See section 6.3.

6.5 Nature and contents of container

PEXALI 100: 10 ml clear, colourless, Type I glass vial with a grey butyl rubber stopper and sealed with an aluminium-plastic flip-off cap. Single vial packs.

PEXALI 500: 50 ml clear, colourless, Type I glass vial with a grey butyl rubber stopper and sealed with an aluminium-plastic flip-off cap. Single vial packs.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparation

1. Use appropriate aseptic technique during the reconstitution and further dilution of PEXALI for intravenous infusion administration.
2. Calculate the dose and the number of PEXALI vials needed.
3. Reconstitute each PEXALI 100 vial with 4,2 ml of 0,9 % sodium chloride injection, without preservative, resulting in a solution containing approximately 25 mg/ml PEXALI (see section 6.2 for incompatibilities). Slowly add the diluents to the vial and gently swirl each vial until the powder is completely dissolved. **Further dilution is required.**
4. Reconstitute each PEXALI 500 vial with 20 ml of 0,9 % sodium chloride injection, without preservative, resulting in a solution containing approximately 25 mg/ml

PEXALI. Slowly add the diluent to the vial and gently swirl each vial until the powder is completely dissolved. **Further dilution prior to infusion is required.**

5. The appropriate volume of reconstituted PEXALI solution must be further diluted to 100 ml with 0,9 % sodium chloride injection, without preservative. The bag should be gently inverted to mix the solution to obtain a homogeneous solution.
6. PEXALI infusion solution must be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.
7. PEXALI solution should then be administered by intravenous infusion over 10 minutes.
8. PEXALI solutions are for single use only. Any unused medicinal product or waste material must be disposed of in accordance with local requirements.

Handling

Procedures for proper handling and disposal should be observed. Care should be exercised in the handling and preparation of infusion solutions of PEXALI.

The use of gloves is recommended. If PEXALI solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If PEXALI solutions contact the mucous membranes, flush thoroughly with water. PEXALI is not a vesicant. There is not a specific antidote for extravasation of PEXALI. Extravasation should be managed by local standard practice as with other non-vesicants.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBERS

PEXALI 100: 51/26/0518.516

PEXALI 500: 51/26/0519.517

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

20 October 2020

10. DATE OF REVISION OF TEXT

May 2023