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

Macleods Pharmaceuticals SA (Pty) Ltd.
Office Block 1, Bassonia Estate Office Park (East),
1 Cussonia Drive, Bassonia Rock, Ext 12, Alberton.
Tel: +27 11 682 1169

8. REGISTRATION NUMBERS

PEXALI 100: 51/26/0518
PEXALI 500: 51/26/0519

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

20 October 2020

10. DATE OF REVISION OF TEXT

May 2023

PATIENT INFORMATION LEAFLET

Scheduling status: S4

PEXALI® 100, powder for concentrate for solution for infusion
PEXALI® 500, powder for concentrate for solution for infusion

Pemetrexed
Contains sugar (mannitol)

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

Read all of this leaflet carefully before you are given PEXALI
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other healthcare provider.
- PEXALI has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet

1. What PEXALI is and what it is used for
2. What you need to know before you use PEXALI
3. How to use PEXALI
4. Possible side effects
5. How to store PEXALI
6. Contents of the pack and other information

1. What PEXALI is and what it is used for
Pemetrexed is an anticancer medicine that inhibits the growth of cancer cells and may reduce tumour size.
PEXALI is used in the treatment for malignant pleural mesothelioma (a type of cancer which affects the lining of the chest cavity). It is given in combination with cisplatin, which is another anticancer medicine.
PEXALI may also be given for advanced stage lung cancer (a certain type, called non-small cell lung cancer) after other anticancer medicines have been used.

2. What you need to know before you use PEXALI
Do not use PEXALI
- if you are hypersensitive (allergic) to pemetrexed or any of the other ingredients of PEXALI (listed in section 6);
- if you have recently received or are about to receive a vaccine against yellow fever.

Warnings and precautions
Special care should be taken with PEXALI.
Tell your doctor or healthcare provider before being given the injection:
- if you currently have, or have previously had, problems with your kidneys, as you may not be able to receive PEXALI;
- if you have heart disease or a history of heart disease;
- if you have recently been vaccinated, as this can cause adverse effects with PEXALI (see "Other medicines and PEXALI");
- if you have an accumulation of fluid around your lungs, your doctor may decide to remove the fluid before giving you PEXALI;
- if you have had or are going to have radiation therapy, please tell your doctor, as there may be an early or late radiation reaction with PEXALI;
- if you are taking NSAIDs (nonsteroidal anti-inflammatory drugs) (see "Other medicines and PEXALI").

While you are treated with PEXALI your doctor will perform regular blood tests to monitor changes in your blood count (see section 4). Your doctor may decide to change the dose or delay treating you depending on your general condition and if your blood cell counts are too low.
If you are also receiving cisplatin, your doctor may make sure that you are properly hydrated and receive appropriate treatment before and after receiving cisplatin to prevent vomiting (feeling sick).
If any of the above applies to you (or you are not sure), consult your doctor, pharmacist or healthcare professional before you are given PEXALI.
Children and adolescents
PEXALI is not indicated for treatment of children under 18 years.
Other medicines and PEXALI
Always tell your healthcare provider if you are taking any other medicine. (This includes all complementary or traditional medicines).
Tell your doctor if you are taking, or have received the following medicines which may delay the removal of PEXALI or increase the occurrence of side effects:
- nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, aspirin, piroxicam, rofecoxib. If your kidney function is impaired, NSAIDs should be avoided at least 2 days before, on the day of, and at least 2 days after PEXALI administration;
- Ciclosporin (an immunosuppressant medicine);
- Aminoglycoside antibiotics such as streptomycin, kanamycin, tobramycin, amikacin and penicillin;
- probenecid (medicine to prevent gouty arthritis);
- platinum compounds (such as cisplatin, carboplatin) also used in cancer treatment;
- 'water pills' (loop diuretics) such as furosemide.

Tell your doctor or pharmacist if you are currently using the following medicines, since PEXALI may affect how well these medicines work:
- anticoagulants (medicines to prevent blood clotting), such as warfarin. Your doctor may require more frequent blood tests as oral anticoagulants and anticancer medicines may have an interaction.
- vaccines, particularly yellow fever vaccine
- any other vaccines (medicines to make your immune system learn to fight an infectious disease).

Pregnancy, breastfeeding and fertility
Pregnancy
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other healthcare provider for advice before receiving PEXALI.
PEXALI should be avoided during pregnancy due to the potential risk to the foetus. Your doctor will explain to you the potential risk of receiving PEXALI during pregnancy.
Women should avoid becoming pregnant during treatment with PEXALI and must use effective contraception during the treatment.
Breastfeeding
You should not breastfeed your baby while receiving PEXALI because it could affect your baby.
Fertility
Men should not father a child during and up to 6 months following treatment with PEXALI. Effective contraception should be used during treatment with PEXALI and for up to 6 months afterwards. If you would like to father a child during the treatment or in the 6 months following receipt of treatment, seek advice from your doctor or pharmacist. You may want to get expert advice on sperm storage before you start chemotherapy with PEXALI.
Driving and using machines
PEXALI may make you feel tired and dizzy (see section 4).
Therefore, you should not drive or use machines until you know how PEXALI will affect you.
PEXALI contains sodium
PEXALI 100 contains 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 vial.
You should take this into consideration if you are on a controlled sodium diet.

3. How to receive PEXALI
Do not share medicines prescribed for you with any other person.
You will not be expected to give PEXALI to yourself. It will be given to you by a person who is qualified to do so.
PEXALI will be administered to you in a specialised unit in hospital.
The usual dose of PEXALI is 500 mg/m^2.
Your doctor will work out what dose you should receive. He/she will consider your diagnosis, your weight and height and kidney function. The dose may be adjusted, or treatment may be delayed depending on your blood cell counts and your general condition.
Your doctor will decide how long your treatment with PEXALI solution for infusion will last.
After appropriate preparation and further dilution with a sterile saline solution, PEXALI will be infused (dripped) into a large vein. The infusion will last approximately 10 minutes. You should usually receive your infusion every 21 days (3 weeks).

Additional medicines
When using PEXALI in combination with cisplatin:
The doctor or hospital pharmacist will work out the dose you need based on your height and weight. Cisplatin is also given by infusion into one of your veins and is given approximately 30 minutes after the infusion of PEXALI has finished. The infusion of cisplatin will last approximately 2 hours.
Corticosteroids:
It is recommended that you take steroid tablets (equivalent to 4 mg of dexamethasone twice a day) on the day before, on the day of, and on the day after PEXALI treatment. This medicine is given to you to reduce the frequency and severity of skin reactions that you may experience during your anticancer treatment.
Vitamin supplementation:
You should also take oral folic acid or a multivitamin containing folic acid (350 to 1 000 micrograms) once a day while you are receiving PEXALI. You should take at least 5 doses during the 7 days before the first dose of PEXALI. You must continue taking the folic acid for 21 days after the last dose of PEXALI. You will also receive an injection of vitamin B_{12} (1 000 micrograms) in the week before administration of PEXALI and then approximately every 2 to 3 months (corresponding to 3 courses of PEXALI treatment). Vitamin B_{12} and folic acid are given to you to reduce the possible toxic effects of the anticancer treatment.

If you have the impression that the effect of PEXALI is too strong or too weak, tell your doctor of pharmacist.

If you receive more PEXALI than you should
Since a healthcare provider will administer PEXALI, he/she will control the dosage. However, in the event of overdosage your doctor will manage the overdosage.
Tell your healthcare provider at once if you think you may have been given too much PEXALI.

If you forget to use PEXALI
Since a healthcare provider will administer PEXALI, it is unlikely that the dose will be missed.

4. Possible side effects
PEXALI can have side effects.
Not all side effects reported for PEXALI are included in this leaflet. Should your general health worsen, or if you experience any untoward effects while receiving PEXALI, please consult your healthcare provider for advice.
If the following happens, stop using PEXALI and tell your doctor immediately or go to the casualty department at your nearest hospital:
- Allergic reactions: swelling of the tongue and/or throat, difficulty in swallowing, difficulties in breathing, facial swelling, severe dizziness and a very fast heartbeat with heavy sweating.
- Allergic skin reactions: severe skin rash, burning or prickling sensation, fever, hives, itching, blistering and peeling of the skin (Stevens-Johnson syndrome or toxic epidermal necrolysis).

These are all very serious side effects. If you have them, you may have had a serious reaction to PEXALI. You may need urgent medical attention or further hospitalisation.
Tell your doctor immediately if you notice any of the following:
- Fever or infection: if you have a temperature of 38 °C or greater, sweating or other signs of infection (since you might have less white blood cells than normal). Infection (sepsis) may be become severe and could be fatal.
- Skin infections (red, swollen, warm skin). You may have a bacterial infection and need additional medicines.
- Red, inflamed skin (erythema multiforme – an allergic skin condition).
- Sudden breathlessness, intense chest pain or cough with bloody sputum. These symptoms may indicate a blood clot in the blood vessels of the lungs.
- Heart attacks, chest pain (angina), irregular heart rate.
- Strokes or "mini-strokes", usually in combination with another anticancer therapy.
- Bleeding from the gums, nose or mouth or any bleeding that would not stop, reddish or pinkish urine, unexpected bruising (due to a low platelet count).
- Colitis (inflammation of the lining of the large bowel, which may be accompanied by intestinal or rectal bleeding).
- Drowsiness, thirst, nausea and decreased or no urine (this could be due to damage to the cells in the small tubes of the kidneys).
- Acute renal failure (decreased urinary output, swelling, fatigue).

These are all serious side effects. You may need urgent medical attention.
Tell your doctor if you notice any of the following:
Frequent side effects:
- low haemoglobin level (anaemia)
- decreased white blood cells
- decreased platelets (blood clotting problems)
- dehydration (feeling tired and thirsty) (in combination with cisplatin)
- loss of sensation (sensory neuropathy)
- taste change
- red, inflamed eyes (conjunctivitis) (in combination with cisplatin)
- nausea
- vomiting
- diarrhoea
- anorexia (eating disorder)
- constipation
- pain, redness, swelling or sores in your mouth
- dyspepsia (heartburn) (in combination with cisplatin)
- hair loss
- skin rash
- peeling of the skin
- kidney disorders (shown by abnormal blood tests)
- fatigue (tiredness)
- liver problems: abnormal blood tests
- increased skin pigmentation
- oedema (excess fluid in body tissue, causing swelling)
- fever.

Less frequent side effects:
- dizziness
- muscle weakness (motor neuropathy)
- haemolytic anaemia (red blood cells are destroyed faster than they can be made)
- peripheral arterial disease (a circulatory problem in which narrowed arteries cause bad circulation and could cause death of tissues in hands or feet)
- conjunctivitis (red, sore eyes), watery eyes
- inflammation of the lining of the oesophagus (gullet) if you have also received radiation therapy
- interstitial pneumonitis (scarring and inflammation of the tissue that surrounds the lung's air sacs, blood vessels and airways)
- radiation recall (a skin rash like severe sunburn) which can occur on skin that has previously been exposed to radiotherapy, from days to years after the radiation
- pancytopenia – combined low counts of white cells, red cells and platelets
- radiation pneumonitis (scarring of the air sacs of the lung associated with radiation therapy) may occur in patients who are also treated with radiation either before, during or after their PEXALI therapy.

Frequency unknown:
- skin infections
- thirst with large volumes of urine (diabetes insipidus)
- lower limb swelling with pain and redness.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.
Reporting of side effects
If you get side effects, talk to your doctor, pharmacist or nurse. You can also report side effects to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: **https://www.sahpra.org.za**. By reporting side effects, you can help provide more information on the safety of PEXALI.

5. How to store PEXALI
Store all medicines out of reach of children.
Store the vial in the original container, at or below 25 °C. Do not freeze.
Reconstituted and infusion solutions: The product should be used immediately. When prepared as directed, chemical and physical in-use stability of reconstituted and infusion solutions of PEXALI 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.
PEXALI is for single use only; any unused solution must be disposed of in accordance with local requirement.
The expiry date is stated on the label and carton. Your healthcare professional will make sure that PEXALI is not past its expiry date before giving you the injection.

6. Contents of the pack and other information
What PEXALI contains
- The active substance is pemetrexed.

PEXALI 100: Each vial contains 100 milligrams of pemetrexed (as pemetrexed disodium 2,5 hydrate).
PEXALI 500: Each vial contains 500 milligrams of pemetrexed (as pemetrexed disodium 2,5 hydrate).
PEXALI contains:
- about 11 mg sodium per 100 mg vial (essentially 'sodium-free')
- approximately 54 mg of sodium per 500 mg vial.

The other ingredients are mannitol, hydrochloric acid and sodium hydroxide.
Further dilution by a healthcare provider is required prior to administration.
What PEXALI looks like and contents of the pack
White to faint yellow lyophilized cake or powder.
The reconstituted solution is a clear, colourless solution without visible particles.
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.

Holder of the Certificate of Registration
Macleods Pharmaceuticals SA (Pty) Ltd.
Office Block 1, Bassonia Estate Office Park (East),
1 Cussonia Drive, Bassonia Rock, Ext 12, Alberton.
Tel: +27 11 682 1169

This leaflet was last revised in
May 2023

Registration numbers
PEXALI 100: 51/26/0518
PEXALI 500: 51/26/0519

INLIGTINGSPAMFLET VIR DIE PASIËNT

Skeduleringstatus: S4

PEXALI® 100, poeier vir konsentraat vir oplossing vir infusie
PEXALI® 500, poeier vir konsentraat vir oplossing vir infusie

Pemetreksed
Bevat suiker (mannitol)

PEXALI 100 bevat 106,4 mg mannitol per flessie en PEXALI 500 bevat 500 mg mannitol per flessie.

Lees die hele pamflet sorgvuldig deur voordat PEXALI aan jou gegee word
- Hou hierdie pamflet. Dit is moontlik dat jy dit weer sal wil lees.
- Indien jy nog vrae het, raadpleeg asseblief jou dokter, apteker, verpleegster of ander gesondheidsorgverskaffer.
- PEXALI is vir jou persoonlik voorgeskryf en jy moet nie jou medisyne met ander mense deel nie. Dit kan skadelik vir hulle wees, selfs al is hulle simptome dieselfde as joune.

Wat is in hierdie pamflet

1. Wat PEXALI is en waarvoor dit gebruik word
2. Wat jy moet weet voordat jy PEXALI gebruik
3. Hoe om PEXALI te gebruik
4. Moontlike newe-effekte
5. Hoe om PEXALI te bewaar
6. Inhoud van die pakkie en ander inligting

1. Wat PEXALI is en waarvoor dit gebruik word
Pemetreksed is 'n anti-kanker medisyne wat die groei van kankerselle inhibeer en die grootte van die gewas kan verminder.
PEXALI word gebruik by die behandeling van kwaadaardige pleurale mesotelioom ('n tipe kanker wat die voering van die borsholte aantas). Dit word in kombinasie met sisplatien, 'n ander anti-kanker medisyne, gebruik.
PEXALI kan ook vir gevorderde stadium longkanker ('n sekere tipe, genoem nie-kleinsellige longkanker) gegee word nadat ander anti-kanker medisynes gebruik is.

2. Wat jy moet weet voordat jy PEXALI gebruik
Moenie PEXALI gebruik nie
- as jy hipersensitief (allergies) is vir pemetreksed of vir enige van die ander bestanddele van PEXALI (gelys in afdeling 6);
- as jy onlangs 'n entstof teen geelkoors ontvang het, of op die punt staan om dit te ontvang.

Waarskuwings en voorsorgmaatreëls
Spesiale sorg moet gedra word met PEXALI.
Sê vir jou dokter of gesondheidsorgverskaffer voordat jy die inspuiting ontvang:
- as jy tans of voorheen probleme met jou niere het of gehad het, aangesien jy dalk nie PEXALI sal kan ontvang nie;
- as jy hartsiektes het of 'n geskiedenis van hartsiekte het;
- as jy onlangs ingeënt is, aangesien dit newe-effekte kan veroorsaak met PEXALI (kyk "Ander medisynes en PEXALI");
- as jy 'n ophoping van vloeistof om jou longe het kan jou dokter besluit om die vloeistof eers te verwyder voordat PEXALI aan jou gegee word;
- as jy bestralingsterapie gehad het of gaan kry, moet jy dit asseblief vir jou dokter sê, want daar kan moontlik 'n vroeë of laat bestralingsreaksie met PEXALI wees;
- as jy NSAIM's (nie-steroïdale anti-inflammatoriese middels) neem (kyk "Ander medisynes en PEXALI").

Terwyl jy met PEXALI behandel word, sal jou dokter gereeld bloedtoetse doen om veranderinge in jou bloedtelling te moniteer (kyk afdeling 4). Jou dokter kan besluit om die dosis te verander of behandeling te vertraag, afhangende van jou algemene welstand en of jou bloedseltellings te laag is.
As jy ook sisplatien ontvang kan jou dokter seker maak dat jy behoorlik gehidreer is en dat jy voor en na die ontvangs van sisplatien die geskikte behandeling ontvang om braking (opbring) te voorkom.
Indien jy nie seker is of enige van die bogenoemde op jou van toepassing is nie, praat met jou dokter, apteker of gesondheidsorgkundige voordat jy PEXALI neem.
Kinders en adolessente
PEXALI is nie aangedui vir die behandeling van kinders onder 18 jaar oud nie.
Ander medisynes en PEXALI
Lig altyd jou gesondheidsorgverskaffer in as jy enige ander medisyne neem. (Dit sluit alle komplementêre of tradisionele medisyne in).
Sê vir jou dokter as jy die volgende medisyne neem of ontvang het. Hierdie medisynes kan die verwydering van PEXALI vertraag of die voorkoms van newe-effekte verhoog:
- nie-steroïdale anti-inflammatoriese medisynes (NSAIM's) soos ibuprofeen, aspirien, piroksikaam, rofekoksib. Indien jou nierfunksie verswak is, moet NSAIM's vir ten minste 2 dae voor die tyd, op die dag van toediening, of 2 dae na die toediening van PEXALI vermy word;
- Siklosporien ('n immuunonderdrukkende medisyne);
- Aminoglikosied-antibiotika soos streptomisien, kanamisien, tobramisien, amikasien en penisillien;
- probenesied (medisyne om jigartritis te voorkom);
- platinumverbindings (soos sisplatien, karboplatien) wat ook by kankerbehandeling gebruik word;
- 'waterpille' (lusdiuretika) soos furosemied.

Lig jou dokter of apteker in as jy tans die volgende medisynes gebruik, aangesien PEXALI die werking van hierdie medisynes kan affekteer:
- antistolmiddels (medisynes wat gebruik word om bloedklonte te voorkom), soos warfarien. Jou dokter kan meer gereeld bloedtoetse benodig, aangesien orale antistolmiddels en anti-kanker medisynes 'n interaksie kan hê.
- entstowwe, in besonder geelkoorsentstof.
- enige ander entstowwe (medisynes wat jou immuunstelsel leer om 'n aansteeklike siekte te beveg).

Swangerskap, borsvoeding en vrugbaarheid
Swangerskap
Indien jy swanger is of borsvoed, dink jy is dalk swanger, of beplan om 'n baba te hê, raadpleeg asseblief jou dokter, apteker of ander gesondheidsorgverskaffer voordat jy PEXALI ontvang.
PEXALI moet tydens swangerskap vermy word vanweë die moontlike risiko aan die fetus. Jou dokter sal aan jou die moontlike risiko om PEXALI tydens swangerskap te ontvang verduidelik.
Vrouens moet vermy om swanger te raak tydens behandeling met PEXALI en moet doeltreffende voorbehoedmiddels gebruik tydens die behandeling.
Borsvoeding
Jy moet nie jou baba borsvoed terwyl jy PEXALI ontvang nie, want dit kan jou baba affekteer.
Vrugbaarheid
Mans moet nie 'n kind tydens die behandeling en tot 6 maande na behandeling met PEXALI verwek nie. Doeltreffende voorbehoeding moet tydens die behandeling met PEXALI en vir tot 6 maande daarna gebruik word. As jy 'n kind wil verwek tydens die behandeling of in die 6 maande na ontvangs van behandeling, raadpleeg jou dokter of apteker. Jy mag moontlik deskundige raad wil inwin oor die opberging van sperma voordat jy chemoterapie met PEXALI begin.
Bestuur en gebruik van masjinerie
PEXALI kan jou moeg en duiselig maak (kyk afdeling 4).
Jy moet dus nie bestuur of masjinerie gebruik voordat jy nie weet hoe PEXALI jou gaan affekteer nie.
PEXALI bevat natrium
PEXALI 100 bevat 11 mg (minder as 1 mmol) natrium per 100 mg flessie en dit is in wese 'natriumvry'.
PEXALI 500 bevat ongeveer 54 mg natrium per flessie.
As jy op 'n gekontroleerde natriumdieet is moet jy dit in ag neem.

3. Hoe om PEXALI te ontvang
Moenie medisyne wat vir jou voorgeskryf is met enige ander persoon deel nie.
Daar sal nie van jou verwag word om PEXALI aan jouself toe te dien nie. Dit sal aan jou gegee word deur 'n persoon wat gekwalifiseer is om dit te doen.
PEXALI sal in 'n gespesialiseerde eenheid in 'n hospitaal aan jou toegedien word.
Die gewone dosis van PEXALI is 500 mg/m^2.
Jou dokter sal uitwerk watter dosis jy moet ontvang. Hy/sy sal jou diagnose, gewig en lengte en nierfunksie in ag neem. Die dosis kan aangepas word, of die behandeling kan vertraag word, afhangende van jou bloedseltellings en jou algemene siektetoestand.
Jou dokter sal besluit hoe lank jou behandeling met PEXALI oplossing vir infusie sal duur.
Na geskikte voorbereiding en verdere verdunning met 'n steriele soutoplossing, word PEXALI in 'n groot aar toegedien (gedrup). Die infusie sal ongeveer 10 minute duur. Jy sal gewoonlik jou infusie elke 21 dae (3-weekliks) ontvang.

Aanvullende medisynes
Wanneer PEXALI in kombinasie met sisplatien gebruik word:
Die dokter of hospitaalapteker sal die dosis wat jy benodig, uitwerk op grond van jou lengte en gewig. Sisplatien word ook deur infusie in een van jou are gegee en dit word ongeveer 30 minute nadat die infusie met PEXALI afgehandel is, gegee. Die infusie van sisplatien sal ongeveer 2 uur duur.
Kortikosteroïede:
Dit word aanbeveel dat jy steroïedtablette (gelykstaande aan 4 mg deksametasoon twee keer per dag) neem op die dag voor, op die dag van, en op die dag na die behandeling met PEXALI. Hierdie medisyne word aan jou gegee om die frekwensie en erns van velreaksies wat jy tydens jou kankerbehandeling kan ervaar, te verminder.
Vitamienaanvulling:
Jy moet ook mondelike foliensuur, of 'n multivitamien wat foliensuur (350 tot 1 000 mikrogram) bevat, een keer per dag neem terwyl jy PEXALI ontvang. Jy moet minstens 5 dosisse gedurende die 7 dae voor die eerste dosis van PEXALI neem. Jy moet vir 21 dae na die laaste dosis van PEXALI aanhou om die foliensuur te neem. Jy sal ook 'n inspuiting van vitamien B_{12} (1 000 mikrogram) in die week voor toediening van PEXALI ontvang en dan ongeveer elke 2 tot 3 maande (wat ooreenstem met 3 kursusse van PEXALI behandeling). Vitamien B_{12} en foliensuur word aan jou gegee om die moontlike toksiese effekte van die anti-kanker behandeling te verminder.
Indien jy die indruk kry dat die effek van PEXALI te sterk of te swak is, lig jou dokter of apteker in.

Indien jy meer PEXALI ontvang as wat jy moes
Aangesien 'n gesondheidsorgverskaffer PEXALI sal toedien, sal hy/sy die dosis beheer. In geval van oordosering sal jou dokter egter die oordosering behandel.
Lig jou gesondheidsorgverskaffer dadelik in as jy dink dat daar te veel PEXALI aan jou gegee is.

Indien jy vergeet het om PEXALI te gebruik
Aangesien 'n gesondheidsorgverskaffer PEXALI sal toedien, is dit onwaarskynlik dat 'n dosis oorgeslaan sal word.

4. Moontlike newe-effekte
PEXALI kan newe-effekte hê.
Nie alle newe-effekte wat vir PEXALI aangemeld is, word by hierdie pamflet ingesluit nie. Indien jou algemene gesondheid agteruitgaan, of jy enige ongunstige effekte ervaar terwyl jy PEXALI ontvang, raadpleeg asseblief jou gesondheidsorgverskaffer vir advies.
Indien enige van die volgende gebeur, staak die gebruik van PEXALI en stel u dokter onmiddellik in kennis daarvan, of gaan na die ongevalle-afdeling by jou naaste hospitaal:
- Allergiese reaksies: swelling van die tong en/of keel, sukkel om te sluk of asem te haal, swelling van die gesig, erge duiseligheid en 'n baie vinnige hartklop met baie sweet.
- Allergiese velreaksies: erge veluitslag, branderige of prikkelende sensasie, koors, netelroos, jeuk, blase en afskilfering van die vel (Stevens-Johnson-sindroom of toksiese epidermale nekrolise).

Al hierdie newe-effekte is baie ernstig. Indien jy dit ervaar, kan jy moontlik 'n ernstige reaksie op PEXALI hê. Jy kan dringende mediese aandag of verdere hospitalisering benodig.
Lig jou dokter dadelik in as jy enige van die volgende waarneem:
- Koors of infeksie: as jy 'n temperatuur van 38 °C of hoër, sweet of ander tekens van infeksie het (aangesien jy minder witbloedselle as gewoonlik het). Infeksie (sepsis) kan ernstig word en kan noodlottig wees.
- Velinfeksies (rooi, geswelde, warm vel). Jy kan 'n bakteriële infeksie hê en bykomende medisyne benodig.
- Rooi, ontsteekte vel (veelvuldige eriteem - 'n allergiese veltoestand).
- Skielike asemtekort, intense borspyn of hoes met bloederige sputum. Hierdie simptome kan dui op 'n bloedklont in die bloedvate van die longe.
- Hartaanval, borspyn (angina), ongereelde hartklop.
- Beroerte of "mini-beroerte", gewoonlik in kombinasie met 'n ander anti-kankerbehandeling.
- Bloeding van die tandvleis, neus of mond of enige bloeding wat nie wil stop nie, rooierige of pienkerige urien, onverwagte kneusplekke (as gevolg van 'n lae bloedplaatjie-telling).
- Kolitis (ontsteking van die voering van die dikderm, wat gepaard kan gaan met intestinale of rektale bloeding).
- Lomerigheid, dors, naarheid en verminderde of geen urien (dit kan wees vanweë skade aan die selle in die klein buisies van die niere).
- Akute nierversaking (verminderde urinêre uitset, swelling, uitputting).

Hierdie is almal ernstige newe-effekte. Jy kan dringende mediese aandag benodig.
Lig jou dokter in as jy enige van die volgende waarneem:
Gereelde newe-effekte:
- lae hemoglobienvlak (anemie)
- afname in witbloedselle
- afname in bloedplaatjies (probleme met bloedstolling)
- dehidrasie (voel moeg en dors) (in kombinasie met sisplatien)
- verlies aan gevoel (sensoriese neuropatie)
- smaakverandering
- rooi, ontsteekte oë (konjunktivitis) (in kombinasie met sisplatien)
- naarheid
- braking
- diarree
- anoreksie (eetversteuring)
- hardlywigheid
- pyn, rooiheid, swelling of sere in jou mond
- dispepsie (sooibrand) (in kombinasie met sisplatien)
- haarverlies
- veluitslag
- vel skilfer af
- niersiektes (aangetoon met abnormale resultate van bloedtoetse)
- uitputting (moegheid)
- lewerprobleme: abnormale bloedtoetse
- verhoogde pigmentasie van die vel
- edeem (oormatige vloeistof in liggaamsweefsels, wat swelling veroorsaak)
- koors.

Minder gereelde newe-effekte:
- duiseligheid
- spierswakheid (motoriese neuropatie)
- hemolitiese anemie (rooibloedselle word vinniger vernietig as wat hulle vervaardig kan word)
- perifere arteriële siekte ('n probleem met die bloedsomloop waar vernoude are swak sirkulasie veroorsaak en dood van weefsels in hande of voete kan veroorsaak)
- konjunktivitis (rooi, seer oë), waterige oë
- ontsteking in die voering van die esofagus (slukderm) as jy ook bestralingsterapie ontvang het
- interstisiële longontsteking (letsels aan en inflammasie van die weefsel wat die lugsakkies in die longe, die bloedvate en lugweë omring)
- terugkeer van reaksies op bestraling ('n veluitslag wat lyk soos erge sonbrand) wat op vel wat voorheen aan radioterapie blootgestel is, vanaf dae tot jare na die bestraling, kan voorkom
- pansitopenie - gekombineerde lae tellings van witselle, rooiselle en plaatjies
- bestralingspneumonitis (letsels aan die lugsakkies van die long geassosieer met bestralingsterapie) kan voorkom by pasiënte wat ook voor, tydens of na hulle behandeling met PEXALI met bestraling behandel word.

Frekwensie onbekend:
- velinfeksies
- dors met groot volumes urien (diabetes insipidus)
- swelling van die onderbene met pyn en rooiheid

Indien jy enige newe-effekte opmerk wat nie in hierdie pamflet vermeld word nie, lig jou dokter of apteker in.
Aanmelding van newe-effekte
Indien jy newe-effekte ervaar, praat met jou dokter, apteker of verpleegster. Jy kan ook newe-effekte aan SAHPRA rapporteer deur middel van die "**6.04 Adverse Drug Reaction Reporting Form**", wat aanlyn onder SAHPRA se publikasies verskyn: **https://www.sahpra.org.za**. Deur newe-effekte aan te meld, kan jy help om meer inligting oor die veiligheid van PEXALI te verskaf.

5. Hoe om PEXALI te bewaar
Bewaar alle medisyne buite bereik van kinders.
Bewaar die flessie in die oorspronklike houer, by of benede 25 °C. Moenie vries nie.
Hersaamgestelde en infusie-oplossings: Die produk moet onmiddellik gebruik word. Wanneer dit volgens voorskrif voorberei is, is die chemiese en fisiese stabiliteit tydens gebruik van die hersaamgestelde en infusie-oplossings van PEXALI aangetoon vir tot 24 uur na hersamestelling van die oorspronklike flessie wanneer dit in 'n yskas tussen 2 en 8 °C en by of benede 25 °C bewaar word.
PEXALI is slegs vir enkelgebruik; alle ongebruikte oplossing moet mee weggedoen word volgens die plaaslike vereistes.
Die vervaldatum word op die etiket en kartonhouer aangedui. Jou gesondheidsorgkundige sal seker maak dat PEXALI nie na die vervaldatum aan jou toegedien word nie.

6. Inhoud van die pakkie en ander inligting
Wat PEXALI bevat
- Die aktiewe bestanddeel is pemetreksed.

PEXALI 100: Elke flessie bevat 100 milligram pemetreksed (as pemetreksed-dinatrium-2,5-hidraat).
PEXALI 500: Elke flessie bevat 500 milligram pemetreksed (as pemetreksed-dinatrium-2,5-hidraat).
PEXALI bevat:
- ongeveer 11 mg natrium per 100 mg flessie (in wese 'natriumvry')
- ongeveer 54 mg natrium per 500 mg flessie.

Die ander bestanddele is mannitol, soutsuur en natriumhidroksied.
Verdere verdunning deur 'n gesondheidsorgverskaffer word benodig voor toediening.
Hoe PEXALI lyk en wat die inhoud van die pakkie is
Wit tot dofgeel gevriesdroogde koek of poeier.
Die hersaamgestelde oplossing is 'n helder, kleurlose oplossing sonder sigbare deeltjies.
PEXALI 100: 10 ml helder, kleurlose, Tipe I-glasflessie met 'n grys butielrubberprop en verseël met 'n aluminium-plastiek afwipdekseltjie. Een flessie per verpakking.
PEXALI 500: 50 ml helder, kleurlose, Tipe I-glasflessie met 'n grys butielrubberprop en verseël met 'n aluminium-plastiek afwipdekseltjie. Een flessie per verpakking.
Nie alle verpakkingsgroottes word noodwendig bemark nie.

Houer van die Registrasiesertifikaat
Macleods Pharmaceuticals SA (Edms) Bpk
Kantoorblok 1, Bassonia Estate Kantoorpark (Oos)
Cussoniarylaan 1, Bassonia Rock, Uitbr.12, Alberton.
Tel: +27 11 682 1169

Hierdie pamflet was voorheen hersien in
Mei 2023

Registrasienommers
PEXALI 100: 51/26/0518
PEXALI 500: 51/26/0519

Vanita Rajool
Digitally signed by Vanita Rajool
DN: cn=Vanita Rajool, o=Macleods Pharmaceuticals SA (Pty) Ltd., ou=Responsible Pharmacist, email=vanitar@macleodspharma.com, c=ZA
Date: 2024.04.30 13:24:25 +02'00'

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