Approved Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PEXITAZ 100 Powder for solution for infusion

PEXITAZ 500 Powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PEXITAZ 100

Each vial contains 100 mg of pemetrexed (as pemetrexed disodium heptahydrate).

Contains sugar: mannitol 106 mg

Contains approximately 11 mg sodium

PEXITAZ 500

Each vial contains 500 mg of pemetrexed (as pemetrexed disodium heptahydrate).

Contains sugar: mannitol 500 mg

The reconstituted PEXITAZ solution contains 25 mg/ml pemetrexed.

For the full list of excipients, see section 6.1.

Contains approximately 54 mg sodium

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

White to either light yellow or green yellow lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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

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

4.2 Posology and method of administration

PEXITAZ should only be administered under the supervision of a medical practitioner qualified in the use of anti-cancer chemotherapy.
For instructions on dilution of the product before administration, (see section 6.6).

Posology:

Malignant pleural mesothelioma

Combination use with cisplatin:

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

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

Adenocarcinoma of the lung

Single medicine use:

Adults: In patient treated with adenocarcinoma of the lung, the recommended dose of PEXITAZ is 500 mg/m^2 administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

Combination use with cisplatin:

Adults: In patients treated for non-small cell lung cancer: the recommended dose of PEXITAZ is 500 mg/m^2 administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle. The recommended dose of cisplatin is 75 mg/m^2 infused over 2 hours approximately 30 minutes after completion of the PEXITAZ infusion on the first day of each 21-day cycle.

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

Premedication regimen:

To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after PEXITAZ administration. The corticosteroid should be equivalent to 4mg of dexamethasone administered orally twice a day (see section 4.4).

To reduce toxicity, patients treated with PEXITAZ should also receive vitamin supplementation (see section 4.4). Patients must take oral folic acid or a multivitamin containing folic acid (350 to 1000 mcg) on a daily basis. At least 5 daily doses of folic acid must be taken during the 7 days preceding the first dose of PEXITAZ, and dosing should continue during the full course of therapy and for 21 days after the last dose of PEXITAZ. Patients must also receive an intramuscular injection of vitamin B_{12} (1000 mcg) in the week preceding the first dose of PEXITAZ and every 3 cycles thereafter.

***Monitoring*:**

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

Dose Adjustments:

Dose adjustments at the start of a subsequent cycle should be based on nadir haematologic counts or maximum non-haematologic toxicity from the preceding

cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery, patients may be retreated using the guidelines in Tables 1,2 and 3 below which are applicable for PEXITAZ used as a single agent or in combination with cisplatin.

Table 1: Dose Modification Table For PEXITAZ (As A Single Agent Or In Combination) And Cisplatin - Haematologic Toxicities	
Nadir ANC < 500/mm^3 and nadir platelets ≥ 50,000/mm^3	75 % of previous dose PEXITAZ and cisplatin
Nadir platelets ≤ 50,000/mm^3 without bleeding regardless of nadir ANC	50 % of previous dose PEXITAZ and cisplatin
Nadir platelets ≤ 50,000/mm^3 with bleeding[a], regardless of nadir ANC	50 % of previous dose PEXITAZ 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 (excluding neurotoxicity) ≥ Grade 3 treatment should be withheld until resolution to less than or equal to the patient's pre-therapy value. Treatment should be resumed according to the guidelines in Table 2 below.

Table 2: Dose Modification Table For PEXITAZ (As Single Agent Or In Combination) And Cisplatin: Non-Haematologic Toxicities [a, b]		
	Dose of PEXITAZ (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	75% of previous dose	75% of previous dose

hospitalisation (irrespective of grade) or Grade 3 or 4 diarrhoea		
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 pemetrexed and cisplatin is documented in Table 3 below. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is observed.

Table 3: Dose Modification Table For PEXITAZ (As Single Agent Or In Combination) And Cisplatin; Neurotoxicity

CTC * Grade	Dose of PEXITAZ (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

* Common Toxicity Criteria (CTC)

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

Special populations

Elderly: In reported clinical studies, there has been no indication that patients 65 years of age or older are at increased risk of adverse events compared to

patients younger than 65 years old. No dose reductions other than those recommended for all patients are necessary.

Paediatric: PEXITAZ is not recommended for use in patients under 18 years of age, as safety and efficacy has not been established in this group of patients.

Patients with renal impairment (standard Cockcroft and Gault formula or glomerular filtration rate measured by Tc99m-DPTA serum clearance method): Pemetrexed is primarily eliminated unchanged by renal excretion. In reported clinical studies, patients with creatinine clearance of ≥45 ml/min required no dosage adjustments other than those recommended to all patients. There are insufficient data reported on the use of pemetrexed in patients with creatinine clearance below 45 ml/min; therefore the use of PEXITAZ 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

PEXITAZ is administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

For precautions to be taken before manipulating or administering PEXITAZ, instructions on reconstitution and dilution of PEXITAZ before administration **see section 6.6**.

4.3 Contraindication

- PEXITAZ is contraindicated in patients with known hypersensitivity to pemetrexed or to any of the excipients of PEXITAZ listed in section 6.1.
- Pregnancy and breastfeeding (see section 4.6).
- Concomitant yellow fever vaccine (see section 4.5).

4.4 Special warnings and precautions for use

Pemetrexed 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 PEXITAZ 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 overall 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, 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 < 45 ml/min. Therefore the use of PEXITAZ 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 – 79 ml/min) should avoid taking non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, and aspirin (> 1.3 g daily) with short-elimination half-lives for at least 2 days prior to, on the day of, and at least 2 days after administration of PEXITAZ.

All patients eligible for pemetrexed therapy should avoid taking NSAIDs with long elimination half-lives at least 5 days prior to, on the day of, and at least 2 days after pemetrexed administration (see section 4.5).

Serious renal events, including acute renal failure, have been reported with pemetrexed alone or in association with other chemotherapeutic agents. Many of the patients in whom these occurred had underlying risk factors for the development of renal events including dehydration or pre-existing hypertension or diabetes. Nephrogenic diabetes insipidus and renal tubular necrosis were also reported in post marketing setting with pemetrexed alone or with other chemotherapeutic medicines. 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. Thus, drainage of third space fluid collection prior to PEXITAZ treatment in 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 reported. Therefore, patients should receive adequate antiemetic treatment and appropriate hydration prior to and/or after receiving PEXITAZ treatment.

Serious cardiovascular events, including myocardial infarction and cerebrovascular events have been uncommonly reported during clinical studies with pemetrexed, usually when given in combination with another cytotoxic agent. Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors (see section 4.8).

Immunodepressed status is common in cancer patients. As a result, concomitant use of live attenuated vaccines is not recommended (see sections 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 pemetrexed 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 PEXITAZ (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 agents.

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

Excipient Warning:

PEXITAZ 100 contains 11 mg (< 1 mmol) sodium per vial, i.e. it is essentially "sodium-free".

PEXITAZ 500 contains approximately 54 mg (2,35 mmol) sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction

Pemetrexed is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. *In vitro* studies indicated that pemetrexed is actively secreted by OAT3 (organic anion transporter 3). Concomitant administration of nephrotoxic medicines (e.g. aminoglycoside, loop diuretics, platinum compounds, ciclosporin and) could result in delayed clearance of pemetrexed. This combination should be used with caution. If necessary, creatinine clearance should be closely monitored.

Concomitant administration of pemetrexed with OAT3 (organic anion transporter 3) inhibitors (e.g. probenecid, penicillin,proton pump inhibitors (PPIs)) results in

delayed clearance of pemetrexed. Caution should be made when these drugs are combined with pemetrexed. If necessary, creatinine clearance should be closely monitored.

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

In patients with normal renal function (creatinine clearance ≥ 80 mL/min), high doses of non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen > 1600 mg/day) and acetylsalicylic acid at higher dose (≥ 1.3 g daily) may decrease pemetrexed elimination and, consequently, increase the occurrence of pemetrexed adverse events. Therefore, caution should be made when administering higher doses of NSAIDs or acetylsalicylic acid, concurrently with PEXITAZ 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 pemetrexed with NSAIDs (e.g. ibuprofen) with shorter half-lives or acetylsalicylic acid at higher dose should be avoided for 2 days before, on the day of, and 2 days following pemetrexed 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 pemetrexed as in PEXITAZ 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 PEXITAZ administration (see section 4.4). If concomitant administration of NSAIDs is necessary, patients should be monitored closely for

toxicity, especially myelosuppression and gastrointestinal toxicity.

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

Pemetrexed undergoes limited hepatic metabolism. Results from reported *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 cytotoxics

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

Concomitant use contraindicated: Yellow fever vaccine: risk of fatal generalised vaccinale disease (see section 4.3).

Concomitant use not recommended: Live attenuated vaccines (except yellow fever, for which concomitant use is contraindicated): risk of systemic, possibly fatal, disease. The risk is increased in subjects 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

Contraception in males and females

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

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.

Pregnancy

There is no data on the use of pemetrexed as in PEXITAZ in pregnant women. Animal studies have reported reproductive toxicity such as birth defects and other defects on the development of the fetus, the course of gestation and peri and post-development. The potential risk for humans is unknown. Therefore the use of pemetrexed as in PEXITAZ should be avoided during pregnancy due to the potential hazard to the fetus. Women should also be advised to avoid becoming pregnant while being treated with PEXITAZ.

Breastfeeding

It is not known whether pemetrexed is excreted in human milk. Therefore it is not recommended that breast feeding be continued during PEXITAZ therapy.

Fertility

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

4.7 Effects on the ability to drive and use machines

Pemetrexed may cause fatigue. Therefore patients should be cautioned against driving or operating machinery if this occurs.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported undesirable effects related to pemetrexed, whether used as monotherapy or in combination, are bone marrow suppression manifested as anaemia, neutropenia, leukopenia, thrombocytopenia; and gastrointestinal toxicities, manifested as anorexia, nausea, vomiting, diarrhoea, constipation, pharyngitis, mucositis, and stomatitis. Other undesirable effects include renal toxicities, increased aminotransferases, alopecia, fatigue, dehydration, rash, infection/sepsis and neuropathy. Less frequently reported events include Stevens-Johnson syndrome and Toxic epidermal necrolysis.

Following are the reported undesirable effects related to pemetrexed, whether used as monotherapy or in combination as per reported clinical studies and post-marketing:

Tabulated summary of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown**
Infections and infestations	Sepsis		
Blood and lymphatic system disorders	Decreased neutrophils / granulocytes, leucocytes, haemoglobin and platelets.	Pancytopenia	Immune-mediated haemolytic anaemia
Immune system disorders	Allergic reaction/Hypersensitivity,		Anaphylactic shock.
Metabolism and nutrition disorders	Dehydration		

Nervous System disorders	Sensory neuropathy Dysgeusia[h], Motor neuropathy	Cerebrovascular accident Transient ischaemic attack,	
Eye disorders	Eyelid oedema, Conjunctivitis	Increased lacrimation	
Cardiac disorders		Chest pain, supraventricular dysrhythmia, Myocardial infarction angina pectoris.	
Vascular disorders			Peripheral ischaemia

Respiratory, thoracic and mediastinal disorders		Pulmonary embolism interstitial pneumonitis.	
Gastrointestinal disorders	Nausea, vomiting, stomatitis, mucositis/pharyngitis, anorexia, diarrhoea (without colostomy), constipation, dyspepsia/heartburn, abdominal pain.	Colitis (including intestinal and rectal bleeding, sometimes fatal, intestinal perforation, intestinal necrosis and typhlitis), oesophagitis/radiation oesophagitis.	
Hepato-biliary disorders	Increased alanine and aspartate aminotransferase (ALT and AST).	Hepatitis, increased gamma-glutamyl transferase (GGT).	

Skin and subcutaneous tissue disorders	Rash/desquamation, pruritus, alopecia, hyperpigmentation, erythema multiforme	Urticaria.	Bullous conditions including Stevens-Johnson syndrome and toxic epidermal necrolysis which in some, cases were fatal; infectious and non-infectious disorders of the dermis, the hypodermis and/or the subcutaneous tissue (e.g. acute bacterial dermo-hypodermitis, pseudocellulitis, dermatitis).

Renal and urinary disorders	Decreased creatinine clearance, renal disorders (combined term includes increased serum/blood creatinine, decreased glomerular filtration rate, renal failure and renal/genitourinary-other)		Nephrogenic diabetes insipidus, renal tubular necrosis.
General disorders and administration site conditions	Fatigue，fever, pain, Oedema[w],	I	Erythematous oedema mainly of the lower limbs.
Injury, poisoning and procedural complications			Radiation recall, radiation pneumonitis.

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 Reaction Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

A 26: Cytostatic agents.
Pharmacotherapeutic group: Folic acid analogues, ATC code: L01BA04

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

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

Once in the cell, pemetrexed is rapidly and efficiently converted to polyglutamate forms by the enzyme folyl polyglutamate synthase. The polyglutamate forms are retained in cells and are even more potent inhibitor 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 in malignant cells.

5.2 Pharmacokinetic properties:

Pemetrexed has a steady-state volume of distribution of 16,1 litres. Pemetrexed is approximately 81% bound to plasma proteins. Binding was not notably affected by varying degrees of renal impairment. Pemetrexed undergoes limited hepatic metabolism.

Pemetrexed is primarily eliminated in the urine, with 70 % to 90 % of the administered drug being recovered unchanged in urine within the first 24 hours following administration.

Pemetrexed total systemic clearance is 91,8 ml/min and the elimination half-life from plasma is 3,5 hours in patients with normal renal function (creatinine clearance of 90 ml/min). Between patient variability in clearance is moderate at 19,3 %. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration increase proportionally with dose. The pharmacokinetics of pemetrexed are consistent over multiple treatment cycles.
The pharmacokinetic properties of pemetrexed are not influenced by concurrently administered cisplatin. Oral folic acid and intramuscular vitamin B12 supplementation do not affect the pharmacokinetics of pemetrexed.

5.3 Preclinical safety data

Administration of pemetrexed to pregnant mice was reported to result in decreased foetal viability, decreased foetal weight, incomplete ossification of some skeletal structures and cleft palate.

Administration of pemetrexed to male mice was reported to result in reproductive toxicity characterised by reduced fertility rates and testicular atrophy. In a study conducted in beagle dog by intravenous bolus injection for 9 months, testicular findings (degeneration/necrosis of the seminiferous epithelium) have been reported. This suggests that pemetrexed may impair male fertility. Female fertility was not investigated.

Pemetrexed was not mutagenic in either the i*n vitro* chromosome aberration test in Chinese hamster ovary cells, or the Ames test. Pemetrexed has been reported to be clastogenic in the *in vivo* micronucleus test in the mouse.

Studies to assess the carcinogenic potential of pemetrexed have not been reported.

6. Pharmaceutical particulars

6.1 List of excipients

Hydrochloric acid, mannitol, nitrogen pure, sodium hydroxide

6.2 Incompatibilities

PEXITAZ must not be mixed with other medicines except those mentioned in section 6.6.

PEXITAZ is physically incompatible with diluents containing calcium, including Lactated Ringer's Injection, USP and Ringer's Injection, USP and therefore these should not be used.

6.3 Shelf life

Unopened vial:

24 months

Reconstituted and infusion solutions:

Chemical and physical stability of reconstituted and infusion solutions of PEXITAZ were demonstrated for up to 24 hours following initial reconstitution, when stored at 25 °C . From a microbiological point of view, PEXITAZ should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 – 8 °C, unless reconstitution or dilution has taken place in controlled and validated aseptic conditions. When prepared as directed, reconstitution and infusion solutions of PEXITAZ contain no antimicrobial

preservatives (see section 6.6). Discard any unused portion.

6.4 Special precautions for storage

Store at or below 25 °C.

Administer infusion solution within 24 hours after initial reconstitution. Discard unused portion.

6.5 Nature and contents of container

PEXITAZ 100:

Each carton contains a 10 ml colourless tubular vial with grey rubber stopper and sealed with light green F/O both sides clear lacquer coated seal.

PEXITAZ 500:

Each carton contains a 50 ml colourless moulded vial with grey rubber stopper and sealed with light green F/O both sides clear lacquer coated seal.

6.6 Special precautions for disposal and other handling

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of pemetrexed infusion solutions. The use of gloves is recommended. If a pemetrexed solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If pemetrexed solutions contact the mucous membranes, flush thoroughly with water. Pemetrexed is not a vescicant. There is not a specific antidote for extravasation of pemetrexed. There have been a few reported cases of pemetrexed extravasation, which were not assessed as sserious by the investigator. Extravasation should be managed by local standard practice as with other non-vesicants.

Reconstitution and further dilution of PEXITAZ prior to intravenous infusion is only recommended with 0,9 % Sodium Chloride Injection (preservative free). PEXITAZ is compatible with standard polyvinyl chloride (PVC) administration sets and intravenous solution bags.

The PEXITAZ solution must be prepared as follows:

1. Use appropriate aseptic technique during the reconstitution and further dilution of PEXITAZ for intravenous infusion administration.
2. Calculate the dose of PEXITAZ and determine the number of vials needed. Vials contain either 100 mg or 500 mg of PEXITAZ. The vials contain an excess of PEXITAZ to facilitate delivery of label amount.
3. Reconstitute each 100 mg vial with 4, 2 ml of 0, 9 % Sodium Chloride Injection (preservative free). Reconstitute each 500 mg vial with 20 ml of 0, 9 % Sodium Chloride Injection (preservative free). Reconstitution of either size vial gives a solution containing 25 mg/ml PEXITAZ. Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in colour from colourless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted PEXITAZ solution is between 6,6 and 7,8. FURTHER DILUTION IS REQUIRED.
4. An appropriate quantity of the reconstituted PEXITAZ solution must be further diluted into a solution of 0, 9 % Sodium Chloride Injection (preservative free), so that the total volume of solution is 100 ml. The bag should be inverted gently to mix the solution to obtain a homogenous solution.
5. PEXITAZ is administered as an intravenous infusion over 10 minutes.

6. Chemical and physical stability of reconstituted and infusion solutions of PEXITAZ (see section 6.3 Shelf-life).
7. Parenteral products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulate matter is observed, do not administer.
8. Procedures for proper handling and disposal should be observed. Care should be exercised in handling and preparation of infusion solutions of PEXITAZ Discard any unused portion.

7. Holder of Certificate of Registration

RANBAXY PHARMACEUTICALS (PTY) LTD

a Sun Pharma company

14 Lautre Road, Stormill, Ext.1,

Roodepoort, 1724

South Africa

8 Registration number(s)

PEXITAZ 100: 51/26/0231

PEXITAZ 500: 51/26/0232

9. Date of first authorisation/renewal of the authorisation

Date of registration.14 July 2020

10. Date of revision of the text : 30 September 2025