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	50 % of previous dose PEXITAZ and

regardless of nadir ANC	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 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 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 radio sensitising 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) 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 substance that are tubulary secreted (e.g. probenecid, penicillin) could potentially result in delayed clearance of pemetrexed. Caution should be made when these medicines are combined with PEXITAZ. 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:

Infections and infestations

Frequent: Infection, sepsis.

Blood and the lymphatic system disorders

Frequent: Decreased neutrophils / granulocytes, leucocytes, haemoglobin and platelets.

Less frequent: Pancytopenia.

Frequency unknown: Immune-mediated haemolytic anaemia.

Immune system disorders

Frequent: Allergic reaction/hypersensitivity.

Frequency unknown: Anaphylactic shock.

Metabolism and nutrition disorders

Frequent: Dehydration.

Nervous system disorders

Frequent: Sensory neuropathy, dysgeusia, motor neuropathy.

Less frequent: Cerebrovascular accident, transient ischaemic attack.

Eye disorders

Frequent: Conjunctivitis.

Less frequent: Increased lacrimation.

Cardiac disorders

Less frequent: Chest pain, supraventricular dysrhythmia, myocardial infarction, and angina pectoris.

Vascular disorders

Frequency unknown: Peripheral ischaemia

Respiratory, thoracic and mediastinal disorders

Less frequent: Pulmonary embolism, interstitial pneumonitis.

Gastrointestinal disorders

Frequent: Nausea, vomiting, stomatitis, mucositis/pharyngitis, anorexia, diarrhoea (without colostomy), constipation, dyspepsia/heartburn, abdominal pain.

Less frequent: Colitis (including intestinal and rectal bleeding, sometimes fatal, intestinal perforation, intestinal necrosis and typhlitis), oesophagitis/radiation oesophagitis.

Hepato-biliary disorders

Frequent: Increased alanine and aspartate aminotransferase (ALT and AST).

Less frequent: Hepatitis, increased gamma-glutamyl transferase (GGT).

Skin and subcutaneous tissue disorders

Frequent: Rash/desquamation, pruritus, alopecia, hyperpigmentation, erythema multiforme.

Less frequent: Urticaria.

Frequency unknown: 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

Frequent: Decreased creatinine clearance, renal disorders (combined term includes increased serum/blood creatinine, decreased glomerular filtration rate, renal failure and renal/genitourinary-other).

Frequency unknown: Nephrogenic diabetes insipidus, renal tubular necrosis.

General disorders and administration site conditions

Frequent: Fatigue, fever, pain, oedema.

Frequency unknown: Erythematous oedema mainly of the lower limbs.

Injury, poisoning and procedural complications

Frequency unknown: 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 vesicant. 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 serious 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

PROFESSIONAL INFORMATION

SKEDULERINGSTATUS
S4

1. NAAM VAN DIE MEDISYNE
PEXITAZ 100 Poeier vir oplossing vir infusie
PEXITAZ 500 Poeier vir oplossing vir infusie

2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING
PEXITAZ 100
Elke flessie bevat 100 mg pemetreksed (as pemetreksed-dinatriumheptahidraat).
Bevat suiker: mannitol 106 mg
Bevat ongeveer 11 mg natrium
PEXITAZ 500
Elke flessie bevat 500 mg pemetreksed (as pemetreksed-dinatriumheptahidraat).
Bevat suiker: mannitol 500 mg
Die hersaamgestelde PEXITAZ oplossing bevat 25 mg/ml pemetreksed.
Vir ‘n volledige lys van die ander bestanddele, sien seksie 6.1.
Bevat ongeveer 54 mg natrium.

3. FARMASEUTIESE VORM
Poeier vir oplossing vir infusie.
'n Wit tot ligte geel of groen-geel geliofiliseerde poeier.

4. KLINIESE BESONDERHEDE
4.1 Terapeutiese indikasies
PEXITAZ word aangedui vir die behandeling van pasiënte met maligne pleurale mesotelioom in kombinasie met sisplatien.

PEXITAZ word aangedui in kombinasie met sisplatienterapie vir die aanvanklike behandeling van pasiënte met plaaslik gevorderde of metastatiese nie·kleinsellongkanker, behalwe die met oorheersende plaveiselagtige selhistologie.

PEXITAZ word aangedui as monoterapie vir die behandeling van pasiënte met plaasllk gevorderde of metastatiese adenokarsinoom van die long na vorige chemoterapie.

PEXITAZ word aangedui as mono/enkelterapie vir instandhoudingsbehandeling van plaaslik gevorderde of metastatiese adenokarsinoom van die long by pasiënte wie se siekte nle gevorder het nie, onmiddellik na standaard chemoterapie.

4.2 Dosering en metode van toediening
PEXITAZ behoort alleenlik onder die toesig van 'n mediese praktisyn wat in die gebruik van antikankerchemoterapie gekwalifiseer is, toegedien te word.
Vir instruksies vir verdunning van die produk voor toediening daarvan, (sien seksie 6.6).

Dosering:
Maligne pleurale mesotelioom
Gekombineerde gebruik met sisplatien:
Volwassenes: By pasiente wat vir maligne pleurale mesotelioom behandel word, is die aanbevole dosis PEXITAZ 500 mg/m^2 wat as 'n intraveneuse infusie oor 10 minute op die eerste dag van elke 21-dag-siklus toegedien word. Die aanbevole dosis sisplatien is 75

mg/m^2, wat oor 2 uur geïfnfuseer word ongeveer 30 minute na voltooiing van die PEXITAZ-infusie op die eerste dag van elke 21-dag-siklus.
Pasiënte moet toepaslike hidrasie voor, en/of na ontvangs van sisplatien, ontvang.

Adenokarsinoom van die long
Gebruik as enkelmiddel:
Volwassenes: By pasiënte wat vir adenokarsinoom van die long behandel word, is die aanbevole dosis PEXITAZ 500 mg/m^2 wat as 'n intraveneuse infusie oor 10 minute op die eerste dag van elke 21-dag·siklus toegedien word.

Gekombineerde gebruik met sisplatien:
Volwassenes: By pasiënte wat vir nie-kleinsellongkanker behandel word: die aanbevole dosis pemetreksed is 500 mg/m^2 wat as 'n intraveneuse infusie oor 10 minute op die eerste dag van elke 21-dag·siklus, toegedien word. Die aanbevole dosis sisplatien is 75 mg/m^2, wat oor 2 uur geïnfuseer word ongeveer 30 minute na voltooiing van die PEXITAZ-infusie op die eerste dag van elke 21-dag·siklus. Pasiënte moet toepaslike hidrasie voor en/of na ontvangs van sisptatien ontvang.

Premedikasie regimen:
Om die voorkoms en erns van velreaksies te verminder, behoort 'n kortikosteroïed gegee te word die dag voor, op die dag van, en die dag na PEXITAZ-toedlening. Die kortikosteroïed behoort ekwivalent te wees aan 4 mg deksametasoon wat oraal twee keer per dag toegedien word (sien seksie 4.4).

Om toksisiteit te vermlnder, behoort pasiënte wat met PEXITAZ behandel word, ook vitamiensupplementasie te ontvang (sien seksie 4.4). Pasiënte moet orale foliensuur of 'n multivitamien wat foliensuur bevat (350 tot 1000 mkg) op 'n daaglikse basis neem. Ten minste 5 daaglikse dosisse foliensuur moet gedurende die 7 dae voor die eerste dosis PEXITAZ geneem word en dosering behoort voortgesit te word vir die volle terapiekursus en vir 21 dae na die laaste dosis PEXITAZ. Pasiënte moet ook 'n binnespierse inspuiting van vitamien B_{12} (1000 mkg) ontvang in die week voor die eerste dosis PEXITAZ en elke 3 siklusse daama.

Monitering:
Pasiënte wat PEXITAZ ontvang, behoort voor elke dosis gemoniteer te word met 'n vol bloedtelling, insluitend 'n dlfferensiële en 'n plaatjietelling. Periodieke bloedchemietoetse behoort versamel te word om renale en hepatiese funksie te evalueer. Die Absolute neutrofieltelling (ANT) behoort ≥ 1500 selle/mm^3 en plaatjies behoort ≥ 100 000 selle/m^3 te wees voor die begin van elke siklus.

Dosisaanpassings:
Dosisaanpassings aan die begin van 'n volgende siklus behoort gegrond te word op laagtepunt hematologiese tellings of maksimum nie-hematologiese toksisiteit van die voorafgaande terapiesiklus. Behandeling mag vertraag word om voldoende tyd vir herstel toe te laat. Na herstel, mag pasiënte weer behandel word deur van die riglyne in onderstaande Tabelle 1, 2 en 3 gebruik te maak, wat van toepassing is op PEXITAZ wat as ‘n enkelmiddel of in kombinasie met sisplatien gebruik word.

Tabel 1: Dosismodifikasie Tabel vir PEXITAZ (As ‘n enkelmiddel of in kombinasie) en sisplatien – Hematologiese toksisiteite	
Laagtepunt ANT < 500/mm^3 en laagtepunt plaatjies ≥ 50,000/mm^3	75 % van die vorige dosis PEXITAZ en sisplatien

Laagtepunt plaatjies ≤ 50,000/mm^3 sonder bloeding ongeag laagtepunt ANT	50 % van die vorige dosis PEXITAZ en sisplatien
Laagtepunt plaatjies ≤ 50,000/mm^3 met bloeding[a] ongeag laagtepunt ANT	50 % van die vorige dosis PEXITAZ en sisplatien

[a] Hierdie kriteria stem ooreen met die Nasionale Kanker Instituut, Algemene Toksisiteit Kriteria weergawe 2.0 (NCI 1998) definisie van ≥ CTC Graad 2 bloeding.

Indien pasiënte nie-hematologiese toksisiteite (neurotoksisiteit uitgesluit) ≥ Graad 3 ontwikkel, behoort behandellng weerhou te word tot resolusie tot minder as, of gelyk aan die pasiënt se pre-terapie waarde, plaasgevind het. Behandeling behoort dan voortgesit te word volgens die riglyne in onderstaande Tabel 2.

Tabel 2: Dosismodifikasie Tabel vir PEXITAZ (As enkelmiddel of in kombinasie) en sisplatien – Nie-Hematologiese toksisiteite [a, b]

	Dosis PEXITAZ (mg/m^2)	Dosis sisplatien (mg/m^2)
Enige Graad 3 of 4 toksisiteite behalwe mukositis	75 % van die vorige dosis	75 % van die vorige dosis
Enige diarree wat hospitalisasie nodig het (ongeag die graad) of Graad 3 of 4 diarree	75 % van die vorige dosis	75 % van die vorige dosis
Graad 3 of 4 mukositis	50 % van die vorige dosis	100 % van die vorige dosis

[a] Nasionale Kanker Instituut se Algemene Toksisiteit Kriteria (CTC)
[b] Neurotoksisiteit uitgesluit

In 'n geval van neurotoksisiteit, word die aanbevole dosisaanpassing vlr pemetreksed en sisplatien aangedui in onderstaande Tabel 3. Pasiënte behoort teraple te staak indien Graad 3 or 4 neurotoksisiteit waargeneem word.

Tabel 3: Dosismodifikasie Tabel vir PEXITAZ (As 'n enkelmiddel of in kombinasie) en sisplatien – Neurotoksisiteit

CTC * Graad	Dosis PEXITAZ (mg/m^2)	Dosis sisplatien (mg/m^2)
0-1	100 % van die vorige dosis	100 % van die vorige dosis
2	100 % van die vorige dosis	50 % van die vorige dosis

* Algemene Toksisiteit Kriteria (CTC)

Behandeling met PEXITAZ behoort gestaak te word indien 'n pasiënt enige hematologiese of nie-hematologiese Graad 3 of 4 toksisiteit na twee dosisverminderings ondervind of onmiddellik indien Graad 3 of 4 neurotoksisiteit waargeneem word.

Spesiale populasies
Bejaardes. In kliniese studies was daar geen aanduiding dat pasiënte van 65 jaar of ouer aan 'n verhoogde risiko van nadelige reaksies vergeleke met pasiënte jonger as 65 jaar, blootgestel word nie. Geen dosisverminderings, behalwe die wat vir alle pasiënte aanbeveel word, is nodig nie.

Pediatries: PEXITAZ word nie vir gebruik by pasiënte jonger as 18 jaar aanbeveel nie, omdat veiligheid en doeltreffendheid nie by hierdie groep pasiënte vasgestel is nie.

Pasiënte met renale inkorting: (standaard Cockcroft en Gault formule of glomerulêre filtrasietempo gemeet deur Tc99m-DPTA-serumopruimingsmetode): Pemetreksed word primêr onveranderd deur renale uitskeiding geëlimineer. In aangemelde kliniese studies het pasiënte met kreatinienopruiming van ≥ 45 ml/min geen dosisaanpassings, behalwe die wat vlr alle pasiënte aanbeveel word, nodlg gehad nie. Daar is onvoldoende data aangemeld oor die gebruik van pemetreksed by pasiënte met kreatinienopruiming onder 45 ml/min; dus word die gebrulk van PEXITAZ nie aanbeveel nie (sien seksie 4.4).

Pasiënte met hepatiese inkorting: Geen verwantskappe tussen AST (SGOT), ALT (SGPT), of totale bilirubien en pemetreksed -farmakokinetika is geïdentifiseer nie, maar pasiënte met hepatiese inkorting, soos bilirubien > 1,5 keer die boonste limiet van normaal en/of transaminase > 3,0 keer die boonste limiet van normaal (hepatiese metastases afwesig), of > 5,0 keer die boonste limiet van normaal (hepatiese metastases teenwoordig), is nie spesifiek bestudeer nie.

Metode van toediening
PEXITAZ word toegedien as ‘n intraveneuse infusie oor 10 minute op die eerste dag van elke 21-dag siklus.

Vir voorsorg om te neem voor manipulering of toediening van PEXITAZ, instruksies vir hersamestelling en verdunning van PEXITAZ voor toediening, sien seksie 6.6.

4.3 Kontra-indikasies
- PEXITAZ word teenaangedui by pasiënte met bekende hipersensitiwitelt teen pemetreksed of teen enigeen van die ander bestanddele van PEXITAZ (gelys in seksie 6.1).
- Swangerskap en borsvoeding (sien seksie 4.6).
- Gelyktydig met vaksien vir geelkoors (sien seksie 4.5).

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik
Pemetreksed kan beenmurgfunksie onderdruk soos gemanifesteer deur neutropenie, trombositopenie, anemie of pansitopenie (sien seksie 4.8). Mïelo-onderdrukking is gewoonlik die dosisbeperkende toksisiteit. Pasiënte moet vir mïelo-onderdrukking tydens terapie gemoniteer word en PEXITAZ behoort nie aan pasiënte toegedien te word totdat die absolute neutrofieltelling (ANl) tot ≥ 1,500 selle/mm^3 en die plaatjietelling tot ≥ 100,000 selle/mrn^3 terugkeer nie. Dosisverminderings vir daaropvolgende siklusse word gegrond op laagtepunt ANT, plaatjietelling en maksimum nie-hematologiese toksisiteit wat van die vorige siklus waargeneem word (sien seksie 4.2).
Minder algehele toksisiteit en 'n vermindering in Graad 3/4 hematologiese en nie-hematologiese toksisiteite soos neutropenie, koorsneutropenie en infeksie met Graad 3/4 neutropenie is aangemeld toe voorbehandeling met foliensuur en vitamien B_{12} toegedien is. Pasiënte wat met pemetreksed behandel word, moet dus aangeraai word om foliensuur en vitamien B_{12} as 'n profilaktiese maatreël te neem om behandelingsverwante toksisiteit te verminder (sien seksie 4.2).
Velreaksies is aangemeld by pasiënte wat nie vooraf met 'n kortikosteroïed behandel is nie. Voorbehandeling met deksametasoon of 'n ekwivalent kan die voorkoms en erns van velreaksies verminder (sien seksie 4.2).
'n Ontoereikende aantal pasiënte met kreatinienopruiming van < 45 ml/min is bestudeer. Dus word die gebruik van PEXITAZ by pasiënte met kreatinienopruiming van < 45 ml/min nie aanbeveel nie (sien seksie 4.2).
Pasiënte met ligte tot matige renale ontoereikendheid (kreatinienopruiming van 45 - 79 ml/min) behoort die inname van nie-steroïedale anti-inflammatoriese middels (NSAIMs) soos ibuprofeen en aspirin (> 1.3 g daagliks) met kort eliminasie halfleeftye vir ten minste 2 dae voor, op die dag van, of ten rninste 2 dae na toediening van PEXITAZ te vermy.

Alie pasiënte wat vir pemetreksed -terapie geskik is, behoort die inname van NSAIMs met lang eliminasie halfleeftye vir ten minste 5 dae voor, op die dag van, en ten minste 2 dae na toediening van pemetreksed te vermy (sien seksie 4.5).
Ernstige renale voorvalle, insluitend akute renale versaking, is aangemeld met pemetreksed alleen of in assosiasie met ander chemoterapeutiese medisyne. Baie van die pasiënte by wie dit voorgekom het, het onderliggende risikofaktore vir die ontwikkeling van renale voorvalle, insluitend dehidrasie of vooraf bestaande hipertensie of diabetes, gehad. Nefrogeniese diabetes insipidus en renale tubulêre nekrose is ook aangemeld na-bemarking instelling met pemetreksed alleen of met ander chemoterapeutiese medisyne. Meeste van hierdie voovalle het opgeklaar nadat pemetreksed onttrek is. Pasiënte moet gereeld gemoniteer word vir akute tubulêre nekrose, verlaagde nierfunksie en tekens en simptome van nefrogeniese diabetes insipidus (bv. hipernatremie).

Die effek van derde spasie vloeistof, soos pleurale effusie of askites, op pemetreksed is nog nie volledig gedefinïeer nie. Dreinering van versamelings van derde spasie vloeistof voor behandeling met PEXITAZ by pasiënte met normale renale funksie, behoort dus oorweeg te word, maar mag dalk nie nodig wees nie.
As gevolg van die gastroïntestinale toksisiteit van pemetreksed toegedien in kombinasie met sisplatien, is ernstige dehidrasie aangemeld. Pasiënte behoort dus genoegsame antiemetiese behandeling en toepaslike hidrasie te ontvang voor en/of na behandeling met PEXITAZ.

Ernstige kardiovaskulêre voorvalle, insluitend miokardiale infarksie en serebrovaskulêre voorvalle is nie-algemeen aangemeld gedurende kliniese studies met pemetreksed, gewoonlik indien dit in kombinasie met ‘n ander sitotoksiese middel toegedien word. Meeste van die pasiënte by wie hierdie voorvalle aangemeld is, het voorafbestaande kardiovaskulêre risikofaktore gehad (sien seksie 4.8).

Immuunonderdrukking is algemeen by kankerpasiënte. As gevolg hiervan, word gelyktydige gebruik van lewende vaksiene nie aanbeveel nie (sien seksies 4.3 en 4.5).

Pemetreksed kan geneties-skadelike effekte hê. Seksueel volwasse mans word aanbeveel om nie ‘n kind te verwek gedurende en tot 6 maande na behandeling nie. Voorbehoedmaatreëls of onthouding word aanbeveel. As gevolg van die moontlikheid dat pemetreksed-behandeling onomkeerbare onvrugbaarheid kan veroorsaak, word mans aanbeveel om berading te soek aangaande die stoor van sperm voordat behandeling begin word.

Vrouens met die potensiaal om swanger te kan raak moet effektiewe kontasepsie gedurende behandeling met PEXITAZ gebruik (sien seksie 4.6).

Gevalle van radiasie-pneumonitis is aangemeld by pasiënte wat met radiasie behandel is voor, gedurende of net na hul behandeling met pemetreksed. Besondere aandag behoort gegee te word aan hierdie pasiënte en sorg moet geneem word met die gebruik van ander radiosensitiseringsmiddels.

Gevalle van herroeping van radiasie is aangemeld by pasiënte wat radioterapie weke of jare tevore ontvang het.

Waarskuwing oor die ander bestanddele
PEXITAZ 100 bevat 11 mg (< 1 mmol) natrium per flessie, dit is dus in wese “Vry van natrium”.

PEXITAZ 500 bevat ongeveer 54 mg (2,35 mmol) natrium per flessie. Moet in ag geneem word deur pasiënte op ‘n natrium-gekontroleerde dieet.

4.5 Interaksie met ander medisyne en ander vorms van interaksie

Pemetreksed word primêr onveranderd deur die niere uitgeskei as gevolg van glomerulêre filtrasie en tubulêre sekresie. *In vitro* studies dui aan dat pemetreksed aktief deur OAT3 (organiese anioontransporteerder 3) uitgeskei word. Gelyktydige toediening van nefrotoksiese medisyne (bv. aminoglikosiede, lus diuretika, platinumverbindings, siklosporien) kan vertraagde opruiming van pemetreksed tot gevolg hê. Hierdie kombinasie moet met omsigtigheid gebruik word. Indien nodig, behoort kreatinienopruiming noukeurig gemoniteer word. Gelyktydige toediening van stowwe wat tubulêr uitgeskei word (bv. probenesied, penisillien) kan potensieel vertraagde opruiming van pemetreksed tot gevolg hê. Voorsorg moet getref word wanneer hierdie medisyne met PEXITAZ gekombineer word. Indien nodig, behoort kreatinienopruiming noukeurig gemoniteer te word.
Asetielsalisielsuur, wat in lae tot matige dosisse (325 mg oraal elke 6 uur) toegedien word, affekteer nie die farmakokinetika van pemetreksed nie.
By pasiënte met norrnale renale funksie (kreatinienopruiming ≥ 80 ml/min), kan hoë dosisse van nie steroïdale anti-inflammatoriese middels (NSAIMs, soos bv. ibuprofeen > 1600 mg/dag) en asetielsalisielsuur in hoë dosisse (≥ 1.3 g daagliks), mag die eliminasie van pemetreksed verlaag en gevolglik die voorkoms van die newe-effekte van pemetreksed verhoog. Dus moet omsigtigheid gebruik word wanneer hoër dosisse NSAIMs of asetielsalisielsuur gelyktydig met PEXITAZ toegedien word aan pasiënte met normale renale funksie (kreatinienopruiming ≥ 80 ml/min).

By pasiënte met ligte tot matige nierontoereikendheid (kreatinienopruiming van 45 to 79 ml/min), sal die gelyktydige toediening van pemetreksed met NSAIMs (bv. ibuprofeen) met korter eliminasie halfleeftye of asetielsalisielsuur by hoër dosisse vermy moet word vir 2 dae voor, op die dag van, en 2 dae na toediening van pemetreksed (sien seksie 4.4).

In die afwesigheid van data oor die potensiële interaksie met NSAIMs met langer halfleeftye, soos piroksikam of rofekoksib, behoort gelyktydige toediening met pemetreksed, soos in PEXITAZ, by pasiënte met ligte tot matige nierontoereikendheid onderbreek te word vir ten minste 5 dae voor, op die dag van, en ten minste 2 dae na PEXITAZ-toediening. Indien gelyktydige toediening van NSAIMs nodig is, behoort pasiënte noukeurig gemoniteer te word vir toksisiteit, veral miëlo-onderdrukking en gastroïntestinale toksisiteit.

Die farmakokinetika van pemetreksed word nie deur gelyktydig toegediende sisplatien of karboplatien beïnvloed nie. Op soortgelyke wyse word die farmakokinetika van totale platinum nie deur pemetreksed verander nle. Orale foliensuur en binnespierse vitamien B_{12} - supplementasie affekteer nie die farmakokinetika van pemetreksed, soos in PEXITAZ, nie. Pemetreksed ondergaan beperkte hepatiese metabolisme. Resultate van *in vitro* studies met menslike lewermikrosome, het aangedui dat dit voorspel kan word dat pemetreksed nle klinies beduidende inhibisie van die metaboliese opruiming van medisyne wat deur CYP3A, CYP2D6, CYP2C9 en CYP1A2 gemetaboliseer word, sal veroorsaak nie.

<u>Interaksies algemeen vir alle sitotoksiese middels</u>
As gevolg van die verhoogde trombotiese risiko by pasiënte met kanker, is die gebruik van behandeling met antikoagulasie middels algemeen. Die hoë inta-individuele veranderlikheid van die koagulasiestatus gedurende siektes en die moontlikeid van interaksie tussen orale antikoagulante en antikanker chemoterapie, word verhoogde frekwensie van INR (Internationale Normaliseerde Ratio) monitering benodig, indien besluit is om die pasiënt met orale antikoagulante te behandel.

Gelyktydige gebruik wat gekontraindikeerd is: Geelkoors vaksien: risiko van fatale veralgemeende vaksinale siekte (sien seksie 4.3).
Gelyktydige gebruik wat nie aanbeveel word nie: Lewende verswakte entstowwe (behalwe geelkoors, wat gekontraindikeerd is): risiko van sistemiese, moontlik fataal, siekte. Die risiko is hoër by individue wat alreeds immuno-onderdrukking weens hul onderliggende siekte het. Gebruik 'n geïnaktiveerde vaksien waar dit bestaan (poliomiëlitis) (sien seksie 4.4).

4.6 Fertiliteit, swangerskap en laktasie
Kontrasepsie by mans en vrouens
Vrouens wat die potensiaal het om swanger te raak, moet effektiewe kontrasepsie gebruik gedurende behandeling met PEXITAZ.
Pemetreksed kan geneties-skadelike effekte hê. Seksueel volwasse mans word aanbeveel om nie 'n kind te verwek gedurende en tot 6 maande na behandeling nie. Kontraseptiewe maatreëls of onthouding word aanbeveel.

Swangerskap
Daar is geen data oor die gebruik van pemetreksed, soos in PEXITAZ, by swanger vrouens beskikbaar nie. Dierestudies het voortplantingstoksisiteit soos geboortedefekte en ander defekte in die ontwikkeling van die fetus, die verloop van gestasie en voor·en na-ontwikkellng, aangedui. Die potensiële risiko vir die mens is onbekend. Die gebruik van pemetreksed, soos in PEXITAZ, behoort vermy te word tydens swangerskap as gevolg van die potensiële gevaar vir die fetus. Vrouens behoort ook aangeraai te word om swangerskap te vermy terwyl hulle met PEXITAZ behandel word.

Borsvoeding
Dit is nie bekend of pemetreksed in menslike melk uitgeskei word nie. Dit word dus nie aanbeveel dat borsvoeding tydens PEXITAZ-terapie voortgesit moet word nie.

Fertiliteit
As gevolg van die moontlikheid dat behandeling met pemetreksed onomkeerbare onvrugbaarheid mag veroorsaak, word mans aanbeveel om berading te soek aangaande die stoor van sperm voordat behandeling begin word.

4.7 Effek op die vermoë om te bestuur en masjiene te gebruik.
Pemetreksed mag moegheid veroorsaak. Pasiënte moet dus teen bestuur of die gebruik van masjiene gewaarsku word indien dit voorkom.

4.8 Newe-effekte
Opsomming van die veiligheidsprofiel
Die mees algemene newe-effekte verwant aan pemetreksed, of dit as enkelterapie of in kombinasieterapie gebruik is, wat aangemeld is, is: beenmurgonderdrukking wat manifesteer as anemie, neutropenie, leukopenie, trombositopenie en gastroïntestinale toksisiteite wat manifesteer as anoreksie, naarheid, braking, diarree, konstipasie, faringitis, mukositis en stomatitis. Ander newe-effekte sluit in: renale toksisiteite, verhoogde aminotransferases, alopesie, moegheid, dehidrasie, veluitslag, infeksie/sepsis en neuropatie. Minder algemeen aangemelde voorvalle sluit in: Stevens-Johnson-sindroom en Toksiese epidermale nekrolise.

Hierop volg die newe-effekte verwant aan pemetreksed, of dit as enkelterapie of in kombinasieterapie gebruik is, wat aangemeld is in kliniese studies en na bemarking:
Infeksies en infestasies
Algemeen: Infeksie, sepsis.

Bloed- en limfatiese sisteem versteurings
Algemeen: Vermindering van neutrofiele/granulosiete, leukosiete, hemoglobien en plaatjies.
Minder algemeen: Pansitopenie
Frekwensie onbekend: Immuun-gemedieerde hemolitiese anemie.

I**muunsisteem versteurings**
Algemeen: Allergiese reaksie/hipersensitiewiteit.
Frekwensie onbekend: Anafilaktiese skok.

Metabolisme en voedingversteurings
Algemeen: Dehidrasie.

Senuweesisteem versteurings
Algemeen: Sensoriese neuropatie, disgeusie, motor-neuropatie.
Minder algemeen: Serebrovaskulêre ongeluk, kortstondige isgemiese aanval.

Oogversteurings
Algemeen: Konjunktivitis
Minder algemeen: Verhoogde traanvorming

Kardiale versteurings
Minder algemeen: Borspyn, supraventrikulêre disritmie, miokardiale infarksie en angina pektoris.

Vaskulêre versteurings
Frekwensie onbekend: Perifere iskemie.

Respiratoriese, torakale en mediastianale versteurings
Minder algemeen: Pulmonêre embolisme, interstisiële longontsteking.

Gastroïntestinale versteurings
Algemeen: Naarheid, braking. Stomatitis, mukositis/faringitis, anoreksie, diarree (sonder kolostomie), konstipasie, dispepsie/sooibrand, abdominale pyn.
Minder algemeen: Kolitis (insluitende intestinale en rektale bloeding, soms fataal, intestinale perforasie, intestinale nekrose en tiflitis), esofagitis/radiasie esofagitis.

Hepato-bilière versteurings
Algemeen: Verhoogde alanien- en aspartaataminotransferase (ALT en AST).
Minder algemeen: Hepatitis, verhoogde gamma-glutamientransferase (GGT).

Vel en subkutaneuse weefsel versteurings
Algemeen: Veluitslag/afskilfering, pruritus, alopesie, hiperpigmentasie, erythema multiforme.
Minder algemeen: Urtikarie.
Frekwensie onbekend: Bulleuse toestande, insluitend Stevens-Johnson-sindroom en toksiese epidermale nekrolise wat in sommige, gevalle wat fataal was; aansteeklike en nie-aansteeklike versteurings van die dermis, die hipodermis en/of subkutaneuse weefsel (bv. akute bakteriële dermo-hipodermitis, pseudosellulitis, dermatitis).

Renale en urinêre versteurings
Algemeen: Verlaging van kreatinienopruiming, renale versteurings (gekombineerde term sluit in verhoogde serum/bloed kreatinien, verlaagde glomerolêre filtrasiespoed, nierversaking en renale/ genitourinêre- ander).
Frekwensie onbekend: Nefrogeniese diabetes insipidus, renale tubulêre nekrose.

Algemene versteurings en toestande by die toedienigsplek
Algemeen: Moegheid, koors, pyn, edeem.
Frekwensie onbekend: Eritemateuse edeem, hoofsaaklik van die laer ledemate.

Besering, vergiftiging en prosedure komplikasies
Frekwensie onbekend: Herroeping van radiasie, radiasie pneumonitis.

Rapportering van verwagte newe-effekte
Aanmelding van verwagte newe-effekte na magtiging van die medisyne is belangrik. Dit laat voortgaande monitering van die voordeel/risiko-balans van die medisyne toe. Gesondheidsorgverskaffers word gevra om enige verwagte newe-effekte aan te meld aan SAHPRA via die “6.04 Adverse Drug Reaction Reporting Form”, wat aanlyn gevind kan word onder SAHPRA se publikasies: https://www.sahpra.org.za/Publications/Index/8.

4.9 Oordosering
Aangemelde simptome van oordosering sluit neutropenie, anernie, trombositopenie, sensoriese polineutropatie en veluitslag, in. Die verwagte komplikasies van oordosis sluit beenmurgonderdrukking, soos gemanifesteer deur neutropenie, trombositopenie en anemia, in. Daarbenewens mag infeksie met of sonder koors, diarree en/of mukositis, waargeneem word. In geval van vermoede oordosis, behoort pasiënte gemoniteer te word deur middel van bloedtellings en behoort hulle ondersteunende terapie soos nodig te ontvang. Die gebruik van leukovorin in die hantering van pemetreksed -oordosis behoort oorweeg te word.

5. Farmakologiese eienskappe

5.1 Farmakodinamiese eienskappe
A 26: Sitostatiese middels
Farmakoterapeutiese groep: Foliensuur analoë, ATC kode: L01BA04

Pemetreksed Is 'n multiteiken antikanker antifolaatmiddel wat sy werking uitoefen deur onontbeerlike folaat-afhanklike metaboliese prosesse, wat vir selreplikasie noodsaaklik is, te ontwrlg.

Pemetreksed tree op as 'n multiteiken antifolaat deur inhibisie van timidilaatsintase (TS), dihidrofolaatreduktase (DHFA) en glisienamied-ribonukleotied·formieltransferase (GARFT), wat die sleutel fosfaat-afhanklike ensieme vir die *de nova* biosintese van timidien- en purien-nukleotiede is. Pemetreksed word tot binne in selle vervoer deur beide die gereduseerde folaatdraer en membraan-folaatbindende proteïen-transportsisteme.
Nadat dit binne in die sel is, word pemetreksed vinnig en doeltreffend omgesit na pollglutamaatvorms deur die ensiem folielpoliglutamaatsintase. Die poliglutamaatvorms word in selle teruggehou en is nog meer potente inhibeerders van TS en GARFT.
Poliglutamaatvorming is 'n tyd- en konsentrasie-afhanklike proses wat in tumorselle en tot 'n mindere mate, in normale weefsel voorkom. Poliglutamaat-metaboliete het ‘n verhoogde intrasellulêre halfleeftyd wat verlengde werking in maligne selle veroorsaak.

5.2 Farmakokinetiese eienskappe
Pemetreksed het 'n ewewigstoestand volume van distribusie van 16,1 liter. Pemetreksed is ongeveer 81 % aan plasmaproteïene gebonde. Binding is nie merkbaar deur wisselende

grade van nierinkorting beïnvloed nie. Pemetreksed ondergaan beperkte hepatiese metabolisme.

Pemetreksed word hoofsaaklik in die urine uitgeskei en 70 % tot 90 % van die toegediende geneesmiddel word onveranderd in die urine binne die eerste 24 uur na toediening herwin. Die totale sistemiese opruiming van pemetreksed is 91,8 ml/min en d!e eliminasie halfeeftyd uit plasma is 3,5 uur by pasiënte met normale renale funksie (kreatinienopruiming van 90 rnl/mln). Tussen-pasiënt variabiliteit in opruiming is matig teen 19,3 %. Die totale sistemiese blootstelling (AOK) en die maksimum plasmakonsentrasie van pemetreksed neern proporsioneel met dosls toe. Die farmakokinetika van pemetreksed is konsistent oor veelvoudige behandelingsiklusse.
Die farmakokinetiese eienskappe van pemetreksed word nie deur gelyktydig toegediende sisplatien beïnvloed nie. Orale foliensuur en intamuskulêre vitamien B_{12}- supplementasie affekteer nie die farmakokinetika van pemetreksed nie.

5.3 Pre-kliniese veiligheidsdata
Daar is aangemeld dat toediening van pemetreksed aan swanger muise ‘n verlaagde fetale lewensvatbaarheid, verlaagde fetale gewig, onvolledige ossifikasie van sommige skeletstrukture en gesplete verhemelte tot gevolg kan hê.

Daar is aangemeld dat toediening van pemetreksed aan manlike muise reproduktiewe toksisiteit, gekenmerk deur verlaagde vrugbaarheidskoerse en testikulêre atrofie tot gevog kan hê. In ‘n studie gedoen by beagle honde deur intraveneuse bolus-inspuiting vir 9 maande, is testikulêre bevindings (degenerasie/nekrose van die seminale epiteel) aangemeld. Dit dui daarop dat pemetreksed manlike fertiliteit kan benadeel. Vroulike fertiliteit is nie ondersoek nie.

Pemetreksed was nie mutagenies in die *in viro* chromosoom-afwykings toets in Chinese hamster se eierstokselle of die Ames toets nie. Daar is gerapporteer dat pemetreksed klastogenies was in die *in vivo* mikronuleus-toets in muise.
Studies om die karsinogeniese potensiaal van pemetreksed te evalueer, is nie aangemeld nie.

6. Farmaseutiese besonderhede
6.1 Lys van ander bestanddele
Soutsuur, mannitol, suiwer stikstof, natriumhidroksied.

6.2 Onverenigbaarhede
PEXITAZ moet nie met ander middels gemeng word, behalwe met die wat genoem word in seksie 6.6 nie.
PEXITAZ is fisies onverenigbaar met verdunningsmiddels wat kalsium bevat, insluitende Ringer-Laktaat- inspuiting, USP en Ringer- inspuiting, USP, en dus moet hierdie middels nie gebruik word nie.

6.3 Rakleeftyd
Onoopgemaakte flessie:
24 maande
Hersaamgestelde en oplossings vir infusie:
Chemiese en fislese stabiliteit vir die hersaamgestelde oplossings en oplossings vir infusie is gedemonstreer vir tot 24 uur na die aanvanklike hersamestelling, as gestoor by 25 °C. Uit 'n mikrobiologiese oogpunt gesien, behoort PEXITAZ onmiddellik gebruik te word. Indien dit nie onmiddellik gebruik word nie, is die in-gebruik bergingstye en toestande voor gebruik die verantwoordelikheid van die gebruiker en behoort dit gewoonlik nie langer as 24 uur by 2 - 8

°C te duur nle, tensy hersamestelling of verdunning in gekontroleerde en gevalideerde aseptiese toestande plaasgevind het. Indien voorberei soos aangedui, bevat die hersaamgestelde en oplossings vir infusie van PEXITAZ geen antimikrobiese preserveermiddels nie (sien seksie 6.6). Gooi enige ongebruikte gedeelte weg.

6.4 Spesiale voorsorgmaatreëls vir berging

Bewaar by of benede 25 °C.
Dien die oplossing vir infusie binne 24 uur na die aanvanklike hersamestelling toe. Gooi enige ongebruikte gedeelte weg.

6.5 Aard en inhoud van die houer

PEXITAZ 100:
Elke karton bevat ‘n 10 ml kleurlose tubulêre flessie met ‘n grys rubber stopper en is met ‘n ligte groen opknipdoppie, aan beide kante bedek met deursigtige lak, verseël.
PEXITAZ 500:
Elke karton bevat ‘n 50 ml kleurlose gevormde flessie met ‘n grys rubber stopper en is met ‘n ligte groen opknipdoppie, aan beide kante bedek met deursigtige lak, verseël.

6.6 Spesiale voorsorgmaatreëls vir wegdoening en ander hantering

Soos met enige ander potensieel toksiese antikankermiddels, moet sorg gedra word met die hantering en voorbereiding van pemetreksed-oplossings vir infusie. Die gebruik van handskoene word aanbeveel. Indien ‘n pemetreksedoplossing met die vel in aanraking kom, was die vel dadelik en deeglik met seep en water. Indien pemetreksed-oplossings met mukusmembrane in kontak kom, spoel dit deeglik met water. Pemetreksed is nie ‘n middel wat blase vorm nie. Daar is nie ‘n spesifieke teenmiddel vir ekstravasasie van pemetreksed nie. Daar is ‘n paar gevalle van pemetreksedekstravasasie aangemeld wat nie as ernstig beskou is deur die ondersoeker nie. Ekstravasasie moet hanteer word deur lokale standaardpraktyk soos met ander nie-blaasvormende middels.
Hersamestelling en verdere verdunning van PEXITAZ voor intraveneuse infusie, word slegs aanbeveel met 0,9 % Natriumchloried-inspuiting (sonder preserveermiddel).
PEXITAZ is verenigbaar met standaard polivinielchloried (PVC) administrasie stelle en intraveneuse oplossing sakke.
Die PEXITAZ-oplossing moet as volg voorberei word:

1. Gebruik 'n geskikte aseptiese tegniek tydens die hersamestelling en verdere verdunning van PEXITAZ vir intraveneuse infusie toediening.
2. Bereken die dosis van PEXITAZ en bepaal die getal flessies wat benodig word. Die flessies bevat ieder 100 mg of 500 mg PEXITAZ. Die flessies bevat 'n oormaat PEXITAZ om aflewerlng van die hoeveelheid wat op die etiket aangegee word, moontlik te maak.
3. Elke 100 mg flessie moet met 4, 2 ml van ‘n 0, 9 % Natriumchloriedinspuiting (sonder preserveermiddel) hersaamgestel word. Elke 500 mg flessie moet met 20 ml van 'n 0,9 % Natriumchloriedinspuiting (sonder preserveermiddel) hersaamgestel word. Die hersamestelling van albei groottes flessies lewer ‘n oplossing wat 25 mg/ml PEXITAZ bevat. Draai elke flessie versigtig in die rondte totdat die poeier volkome opgelos is. Die oplossing wat hierdeur verkry word is helder en wissel in kleur vanaf kleurloos tot geel of groengeel sonder om die produk se kwaliteit nadelig te beïvloed. Die pH van die hersaamgestelde PEXITAX-oplossing is tussen 6,6 en 7,8. VERDERE VERDUNNING WORD BENODIG.
4. ‘n Toepaslike hoeveelheid van die hersaamgestelde PEXITAZ-oplossing moet verder verdun word met ‘n oplossing van 0.9 % Natriumchloried (sonder preserveermiddel), sodat die totale volume van die oplossing 100 ml is. Die sakkie behoort versigtig omgekeer te word om die oplossing te meng om ‘n homogene oplossing te verkry.
5. PEXITAX word toegedien as ‘n intraveneuse infusie oor 10 minute.

6. Chemiese en fisiese stabiliteit van die hersaamgestelde en die oplossing vir infusie van PEXITAZ (sien seksie 6.3 Rakleeftyd).
7. Parenterale produkte behoort visueel ondersoek te word vir vreemde deeltjies en kleurverandering voor toediening, wanneer die oplossing en die houer dit toelaat. Indien vreemde deeltjies opgemerk word, moet dit nie toegedien word nie.
8. Prosedures vir die geskikte hantering en wegdoening moet toegepas word. Sorg moet uitgeoefen word met die hantering en voorbereiding van infusie-oplossings van PEXITAZ. Enige ongebruikte inhoud van die flessie behoort weggedoen te word.

7. Houer van die Sertifikaat van Registrasie
RANBAXY PHARMACEUTICALS (PTY) LTD
'n Sun Pharma maatskappy
Lautre Weg 14, Stormill, Uitbreiding,
Roodepoort, 1724
Suid Afrika

8. Registrasienommer(s)
PEXITAZ 100: 51/26/0231
PEXITAZ 500: 51/26/0232

9. Datum van eerste magtiging/hernuwing van die magtiging
Datum van registrasie
14 Julie 2020