SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE

PEMJECT 500 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each vial contains pemetrexed disodium hemipentahydrate equivalent to 500 mg pemetrexed.

When reconstituted, PEMJECT solution contains 25 mg/mL pemetrexed.

PEMJECT contains sugar (mannitol, 500 mg)

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

PEMJECT powder for solution for infusion is a white or off-white loose lump or powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

PEMJECT 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.

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

PEMJECT 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

PEMJECT must only be administered by intravenous infusion under the supervision of a medical practitioner qualified in the use of anti-cancer chemotherapy.

Malignant pleural mesothelioma:

Combination use with cisplatin:

Adults: In patients treated for malignant pleural mesothelioma, the recommended dose of PEMJECT 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 PEMJECT infusion on the first day of each 21-day cycle. Patients should receive appropriate hydration prior to and/or after receiving cisplatin.

Adenocarcinoma of the lung:

Single medicine use:

Adults: In patients treated for adenocarcinoma of the lung, the recommended dose of PEMJECT 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 PEMJECT 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 PEMJECT 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 PEMJECT administration. The corticosteroid should be equivalent to 4 mg of dexamethasone administered orally twice a day (see section 4.4).

To reduce toxicity, patients treated with PEMJECT should also receive vitamin supplementation (see section 4.4). Patients must take oral folic acid or a multivitamin containing folic acid (350 to 1 000 *µg*) on a daily basis.

At least 5 doses of folic acid must be taken during the 7 days preceding the first dose of PEMJECT, and dosing should continue during the full course of therapy and for 21 days after the last dose of PEMJECT. Patients must also receive an intramuscular injection of vitamin B_{12} (1 000 *µg*) in the week preceding the first dose of PEMJECT and every 3 cycles thereafter.

Monitoring:

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

Dose adjustments:

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

Table 1: Dose modification table for PEMJECT (as single medicine or in combination) and cisplatin: haematological toxicities	
Nadir ANC < 500/mm^3 and nadir platelets ≥ 50 000/mm^3	75 % of previous dose PEMJECT and cisplatin
Nadir platelets ≤ 50 000/mm^3 without bleeding regardless of nadir ANC	50 % of previous dose PEMJECT and cisplatin
Nadir platelets ≤ 50,000/mm^3 with bleeding [a], regardless of nadir ANC	50% of previous dose PEMJECT 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-haematological toxicities (excluding neurotoxicity) ≥ Grade 3, treatment should be withheld until resolution to less than or equal to the patient's pre-therapy value. Treatment should be resumed according to the guidelines in Table 2.

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

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

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

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

Elderly:

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

Patients with renal impairment (standard Cockcroft and Gault formula or glomerular filtration rate measured by Tc99m-DPTA serum clearance method):

Pemetrexed is primarily eliminated unchanged by renal excretion. Patients with creatinine clearance of ≥ 45 mL/min require no dose adjustments other than those recommended for all patients. There are insufficient data on the use of pemetrexed in patients with creatinine clearance below 45 mL/min; therefore, the use of PEMJECT 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.

Paediatric population:

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

Method of administration

PEMJECT solution should be administered by intravenous infusion over 10 minutes minutes on the first day of each 21-day cycle.

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

4.3 Contraindications

PEMJECT is contraindicated in patients with known hypersensitivity to pemetrexed or to any of the excipients listed in section 6.1.

Concomitant yellow fever vaccine (see section 4.5).

4.4 Special warnings and precautions for use

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 PEMJECT should not be given to patients until absolute neutrophil count (ANC) returns to ≥ 1 500 cells/mm^3 and platelet count

returns to ≥ 100 000 cells/mm^3. Dose reductions for subsequent cycles are based on nadir ANC, platelet count, and maximum non-haematologic toxicity seen from the previous cycle (see section 4.2).

Less toxicity and reduction in Grade 3/4 haematologic and non-haematologic toxicities, such as neutropenia, febrile neutropenia, and infection with Grade 3/4 neutropenia, were reported when pre-treatment with folic acid and vitamin B_{12} was administered. Therefore, all patients treated with PEMJECT 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 PEMJECT in patients with creatinine clearance of < 45 mL/min is not recommended (see section 4.2).

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

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

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

The effect of third-space fluid, such as pleural effusion or ascites, on pemetrexed is not fully defined, therefore, drainage of third-space fluid collection prior to PEMJECT treatment in patients with normal renal function should be considered.

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

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

Immunodepressed status is frequent in cancer patients. Concomitant use of live attenuated vaccines is not recommended (see section 4.3 and 4.5).

Pemetrexed can have genetically damaging effects. Sexually mature males are advised not to father a child during the treatment and up to 6 months thereafter.

Contraceptive measures or abstinence are recommended. PEMJECT treatment may cause irreversible infertility, therefore, men are advised to seek counselling on sperm storage before starting treatment.

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

Radiation pneumonitis has been reported in patients treated with radiation either prior, during or subsequent to their PEMJECT therapy. Particular attention should be paid to these patients and caution exercised with use of other radiosensitising medicines.

Radiation recall has been reported in patients who received radiotherapy weeks or years previously.

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. Pemetrexed is actively secreted by OAT3 (organic anion transporter 3). Concomitant administration of nephrotoxic medicines (e.g.aminoglycosides, loop diuretics, platinum compounds, ciclosporin) could result in delayed clearance of pemetrexed as in PEMJECT. This combination should be used with caution. If necessary, creatinine clearance should be closely monitored.

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

In patients with normal renal function (creatinine clearance ≥ 80 mL/min), high doses of non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen > 1 600 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 PEMJECT to patients with normal function (creatinine clearance ≥ 80 mL/min).

A decrease in pemetrexed clearance occurs following co-administration of PEMJECT with NSAIDs. It is recommended that patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min) should avoid taking NSAIDs with short elimination half-lives at least 2 days before, on the day of, and at least 2 days following administration of PEMJECT (see section 4.4).

In the absence of data regarding potential interaction between pemetrexed as in PEMJECT and NSAIDs having longer half-lives, such as piroxicam, the concomitant administration with PEMJECT 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 PEMJECT administration (see section 4.4). If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression and gastrointestinal toxicity.

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

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

Pemetrexed undergoes limited hepatic metabolism. Pemetrexed as in

PEMJECT would not be predicted to cause significant inhibition of the metabolic clearance of medicines metabolised by CYP3A, CYP2D6, CYP2C9, and CYP1A2.

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 PEMJECT requires 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 patients who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where it exists (poliomyelitis) (see section 4.4).

4.6 Fertility, pregnancy and lactation

Contraception in males and females:

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

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

Pregnancy:

There are no data on the use of pemetrexed as in PEMJECT in pregnant women, but pemetrexed, like other anti-metabolites, is suspected to cause serious birth defects when administered during pregnancy. Animal studies have shown reproductive

defects and other defects on the development of the foetus, the course of gestation toxicity, such as birth and peri- and post-development. The potential risk for humans is unknown. Therefore,the use of PEMJECT should be avoided during pregnancy due to the potential hazard to the foetus. Women should also be advised to avoid becoming pregnant while being treated with PEMJECT.

Lactation:

It is not known whether pemetrexed is excreted in human milk, therefore, it is not recommended that breastfeeding be continued during PEMJECT therapy.

Fertility:

Pemetrexed treatment may cause irreversible infertility, therefore, men are advised to seek counselling on sperm storage before starting treatment.

4.7 Effects on ability to drive and use machines

PEMJECT may cause fatigue. Therefore, patients should be cautioned against driving a vehicle or operating machines if this event occurs.

4.8 Undesirable effects

Patients with malignant pleural mesothelioma (MPM) receiving PEMJECT in combination with cisplatin, supplemented with folic acid and vitamin B_{12}:

System Organ Class	Frequency	Side effects
Infections and infestations	Frequent	Infection
Blood and lymphatic system disorders	Frequent	Decreased: neutrophils/granulocytes, leucocytes, haemoglobin, platelets, febrile neutropenia

Metabolism and nutrition disorders	Frequent	Dehydration
Nervous system disorders	Frequent Less frequent	Sensory neuropathy, dysgeusia Motor neuropathy
Eye disorders	Frequent	Conjunctivitis
Cardiac disorders	Less frequent	Dysrhythmia
Gastrointestinal disorders	Frequent	Nausea, vomiting, stomatitis, pharyngitis, anorexia, diarrhoea, constipation, dyspepsia
Skin and subcutaneous tissue disorders	Frequent	Rash, alopecia, urticaria
Renal and urinary disorders	Frequent	Serum creatinine elevation, decreased creatinine clearance, renal failure
General disorders and administration site conditions	Frequent	Fatigue, pyrexia, chest pain
Investigations	Frequent	Increased AST, ALT, and GGT

Patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) receiving PEMJECT and cisplatin, supplemented with folic acid and vitamin B_{12}:

System Organ Class	Frequency	Side effects
Infections and infestations	Frequent	Infection

Blood and lymphatic system disorders	Frequent	Decreased: haemoglobin, neutrophils/granulocytes, leukocytes, platelets, febrile neutropenia
Metabolism and nutrition disorders	Frequent	Dehydration
Nervous system disorders	Frequent Less frequent	Sensory neuropathy, taste disturbance Motor neuropathy
Eye disorders	Frequent	Conjunctivitis
Cardiac disorders	Less frequent	Dysrhythmia
Gastrointestinal disorders	Frequent	Nausea, vomiting, anorexia, constipation, stomatitis, pharyngitis, diarrhoea without colostomy, dyspepsia/heartburn
Skin and subcutaneous tissue disorders	Frequent	Alopecia, rash/desquamation
Renal and urinary disorders	Frequent	Creatinine elevation, renal failure, decrease creatine clearance
General disorders and administration site conditions	Frequent Less frequent	Fatigue, pyrexia Chest pain
Investigations	Frequent Less frequent	Increased AST, ALT Increased GGT

Patients with locally advanced metastatic non-small cell lung cancer (NSCLC) receiving PEMJECT, supplemented with folic acid and vitamin B_{12} and who

received prior chemotherapy:

System Organ Class	Frequency	Side effects
Infections and infestations	Frequent	Infection without neutropenia
Blood and lymphatic system disorders	Frequent	Decreased: haemoglobin, leucocytes, neutrophils/ granulocytes, platelets, febrile neutropenia
Immune system disorders	Frequent	Allergic reaction/hypersensitivity
Nervous system disorders	Frequent	Motor neuropathy, sensory neuropathy
Cardiac disorders	Less frequent	Supraventricular dysrhythmias
Gastrointestinal disorders	Frequent	Nausea, anorexia, vomiting, stomatitis/pharyngitis, diarrhoea, constipation, abdominal pain
Skin and subcutaneous tissue disorders	Frequent	Rash, desquamation, pruritus, alopecia, erythema multiforme
Renal and urinary disorders	Frequent	Increased creatinine
General disorders and administration site conditions	Frequent	Fatigue, fever
Investigations	Frequent	Increased: AST (SGOT), ALT (SGPT)

Patients with Stage IIIB or 4 non-small cell lung cancer (NSCLC) receiving PEMJECT and who had received prior platinum-based chemotherapy,

supplemented with folic acid and vitamin B_{12}:

System Organ Class	Frequency	Side effects
Infections and infestations	Frequent	Infection, sepsis
Blood and lymphatic system disorders	Frequent Less frequent	Decreased: haemoglobin, leucocytes, neutrophils Decreased platelets, febrile neutropenia, pancytopenia
Immune system disorders	Less frequent	Allergic reaction/hypersensitivity, immune-mediated haemolytic anaemia, anaphylactic shock
Nervous system disorders	Frequent Less frequent	Sensory neuropathy Motor neuropathy
Eye disorders	Frequent	Ocular surface disease (including conjunctivitis), increased lacrimation
Cardiac disorders	Less frequent	Supraventricular dysrhythmia, myocardial infarction, angina pectoris, transient ischemic attack
Vascular disorders	Less frequent	Cerebrovascular accident
Respiratory, thoracic and mediastinal disorders	Less frequent	Interstitial pneumonitis with respiratory insufficiency, radiation pneumonitis
Gastrointestinal disorders	Frequent Less frequent	Nausea, anorexia, vomiting, mucositis, stomatitis, diarrhoea Constipation, colitis (including rectal bleeding, intestinal

		perforation, intestinal necrosis and typhlitis), oesophagitis/radiation oesophagitis
Hepato-biliary disorders	Less frequent	Hepatitis
Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency unknown	Rash, desquamation, hyperpigmentation Alopecia, pruritis/itching, erythema multiforme, bullous conditions (including Stevens-Johnson syndrome and toxic epidermal necrolysis), peripheral ischemia (sometimes leading to extremity necrosis) Erythematous oedema of the lower limbs, infectious and non-infectious disorders of the dermis, hypodermis and/or subcutaneous tissue (e.g. acute bacterial dermo-hypodermitis, pseudocellulitis, dermatitis)
Renal and urinary disorders	Frequent Less frequent Frequency unknown	Renal disorders Decreased creatinine clearance, increased creatinine, decreased glomerular filtration, renal failure Nephrogenic diabetes insipidus, renal tubular necrosis
General disorders and administration site conditions	Frequent	Fatigue, fever, (in the absence of neutropenia), pain, oedema

Injury, poisoning and procedural complications	Less frequent	Radiation recall (in patients who have previously received radiotherapy)
Investigations	Frequent	Increased: AST (SGOT), ALT (SGPT)

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. Health care provders are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms:

Reported symptoms of overdose include neutropenia, anaemia, thrombocytopenia, mucositis, sensory polyneuropathy and rash. Anticipated complications of overdose include bone marrow suppression as manifested by neutropenia, thrombocytopenia and anaemia. In addition, infection with or without fever, diarrhoea and/or mucositis may be seen.

Treatment:

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 PEMJECT overdose should be considered.

5. PHARMACOLOGICAL PROPERTIES

A 26: Cytostatic agents

Pharmacotherapeutic group: Folic acid analogues, ATC code: L01BA04

5.1 Pharmacodynamic properties

Pemetrexed is a multitarget anticancer antifolate medicine 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 key folate-dependent enzymes for the *de novo* biosynthesis of thymidine and purine nucleotides. Pemetrexed is transported into cells by both the reduced folate carrier and membrane folate binding protein transport systems.

Once in the cell, pemetrexed is rapidly and efficiently converted to polyglutamate forms by the enzyme folylpolyglutamate synthase. The polyglutamate forms are retained in cells and are even more potent inhibitors of TS and GARFT. Polyglutamation is a time- and concentration-dependent process that occurs in tumour cells and, to a lesser extent, in normal tissues. Polyglutamated metabolites have an increased intracellular half-life resulting in prolonged 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 dose 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 B_{12} supplementation

do not affect the pharmacokinetics of pemetrexed.

5.3 Preclinical safety data

Administration of pemetrexed, as in PEMJECT, to pregnant mice resulted in decreased foetal viability, decreased foetal weight, incomplete ossification of some skeletal structures and cleft palate.

Administration of pemetrexed to male mice resulted in reproductive toxicity characterised by reduced fertility rates and testicular atrophy. This suggests that pemetrexed may impair male fertility (see section 4.6). Female fertility was not investigated.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol.

Hydrochloric acid and sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

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

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

6.3 Shelf life

Unopened vial

36 months

Reconstituted and infusion solutions

PEMJECT contains no antibacterial preservative.

Chemical and physical in-use stability has been demonstrated for 4 hours at 25 °C.

From a microbiological point of view, PEMJECT 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.

6.4 Special precautions for storage

Store at or below 30 °C.

Do not freeze.

For storage of PEMJECT after reconstitution and dilution, see section 6.3.

6.5 Nature and contents of container

50 mL type I, clear, colourless glass vial, sealed with a 20 mm grey bromobutyl rubber stopper, secured with a 20 mm aluminium seal with a blue flip-off cap, packed in an outer carton.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Precautions to be taken before manipulating or administering PEMJECT

As with other potentially toxic anticancer medicines, care should be exercised in the handling and preparation of PEMJECT infusion solutions. The use of gloves is recommended. If a PEMJECT solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If PEMJECT solutions contact the mucous membranes, flush thoroughly with water. PEMJECT is not a vesicant. There is not a specific antidote for extravasation of PEMJECT. Extravasation should be managed by

local standard practice as with other non-vesicants.

Instructions on reconstitution and dilution of PEMJECT before administration

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

PEMJECT is compatible with standard polyvinyl chloride administration sets and intravenous solution bags.

- Use appropriate aseptic technique during the reconstitution and further dilution of PEMJECT for intravenous administration.
- Calculate the dose and the number of PEMJECT vials needed. The vial contains an excess of PEMJECT to facilitate delivery of label amount.
- Prior to administration, each 500 mg vial must be reconstituted with 20 mL of 0,9 % sodium chloride injection, without preservative, resulting in a solution with a concentration of approximately 25 mg/mL PEMJECT. Slowly add the 0,9 % sodium chloride injection, without preservative, to the vial and gently swirl until the powder is completely dissolved.
- The reconstituted PEMJECT solution must be further diluted with 0,9 % sodium chloride injection, without preservative, prior to intravenous infusion. Further dilute the appropriate volume of the reconstituted PEMJECT solution to 100 mL of 0,9 % sodium chloride injection, without preservative. The bag should be inverted gently to mix the solution to obtain a homogeneous solution.
- After reconstitution, PEMJECT is a clear, light yellow, green solution.
- PEMJECT should be inspected visually for particulate matter and discolouration prior to administration.
- This injection is for single use only and any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OR CERTIFICATE OF REGISTRATION

Lamar International (Pty) Ltd

2 Waterford Mews

Waterford Place

Century City

7441

Cape Town

South Africa

8. REGISTRATION NUMBER

51/26/1066

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

15 June 2020