PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PEMTORI IV 100, powder for solution for infusion

PEMTORI IV 500, powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PEMTORI IV 100: Each vial contains pemetrexed disodium equivalent to 100 mg pemetrexed.

Contains sugar (106,00 mg mannitol per vial)

Reconstitution with 4,2 ml of 0,9 % sodium chloride solution for injection, without preservative, results in a solution containing 25 mg/ml pemetrexed.

PEMTORI IV 500: Each vial contains pemetrexed disodium equivalent to 500 mg pemetrexed.

Contains sugar (500,00 mg mannitol per vial)

Reconstitution with 20 ml of 0,9 % sodium chloride solution for injection, without preservative, results in a solution containing 25 mg/ml pemetrexed.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion

PEMTORI IV 100: A white to light yellow or green yellow lyophilized powder.

PEMTORI IV 500: A white to light yellow or green yellow lyophilized powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of patients with malignant pleural mesothelioma in combination with cisplatin.

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

Monotherapy for the treatment of patients with locally advanced or metastatic adenocarcinoma of the lung after prior chemotherapy.

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

PEMTORI IV should only be administered under the supervision of a medical practitioner qualified in the use of anti-cancer chemotherapy.

Malignant pleural mesothelioma:

Combination use with cisplatin:

Adults: The recommended dose of **PEMTORI IV** 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 **PEMTORI IV** 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 **PEMTORI IV** 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 **PEMTORI IV** 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 **PEMTORI IV** infusion on the first day of each 21-day cycle.

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

Pre-medication regimen:

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

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

Monitoring:

Monitoring, in the form of a with a full blood count, including a differential and platelet count should be undertaken in patients before each dose of **PEMTORI IV**, with periodic blood chemistry tests being 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 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 re-treated using the guidelines in Tables 1, 2 and 3 below, which are applicable for **PEMTORI IV** used as a single medicine or in combination with cisplatin.

Table 1: Dose modification table for PEMTORI IV (as a single medicine or in combination) and cisplatin: Haematologic toxicities

Nadir ANC < 500/mm^3 and nadir platelets ≥ 50 000/mm^3	75 % of previous dose **PEMTORI IV** and cisplatin
Nadir platelets ≤ 50 000/mm^3 without bleeding regardless of nadir ANC	50 % of previous dose **PEMTORI IV** and cisplatin
Nadir platelets ≤ 50 000/mm^3 with bleeding[a] regardless of nadir ANC	50 % of previous dose **PEMTORI IV** 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 a patient develops 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.

Table 2: Dose modification table for PEMTORI IV (as a single medicine or in combination) and cisplatin: Non-haematologic toxicities [a, b]

	Dose of PEMTORI IV (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

	Dose of PEMTORI IV (mg/m^2)	**Dose of cisplatin (mg/m^2)**
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 **PEMTORI IV** 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 PEMTORI IV (as a single medicine or in combination) and cisplatin: Neurotoxicity

CTC* Grade:	**Dose of PEMTORI IV (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

*Common Toxicity Criteria (CTC)

Should a patient experience any haematologic or non-haematologic Grade 3 or 4 toxicity after two dose reductions, treatment should be discontinued. Similarly, immediate discontinuation is recommended should Grade 3 or 4 neurotoxicity be observed.

Special populations

Elderly:

There is no indication that patients 65 years of age or older are at increased risk of adverse events compared to younger patients. No dose reduction of **PEMTORI IV** is required, other than those recommended for all patients.

Patients with renal impairment (Standard Cockcroft and Gault formula or Glomerular Filtration Rate measured Tc99m-DPTA serum clearance method):

Pemetrexed is primarily eliminated unchanged by renal excretion. In 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 on the use of pemetrexed in patients with creatinine clearance below 45 ml/min; therefore, the use of **PEMTORI IV** is not recommended (see section 4.4).

Patients with hepatic impairment:

No relationship 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

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

Method of administration

PEMTORI IV powder for solution for infusion is for single use only.

For Precautions to be taken before handling or administering **PEMTORI IV**, see section 6.6.

PEMTORI IV should be administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

For instructions on reconstitution and dilution of **PEMTORI IV** before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to pemetrexed or to any of the ingredients of **PEMTORI IV** (see section 6.1)
- Concomitant yellow fever vaccine (see section 4.5)

4.4 Special warnings and precautions for use

PEMTORI IV 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 **PEMTORI IV** should not be given to patients until absolute neutrophil count (ANC) returns to ≥ 1500 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).

In patients with mesothelioma, 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 occur when pre-treatment with folic acid and vitamin B12 are administered. Therefore, patients treated with **PEMTORI IV** 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 can occur 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).

Patients with creatinine clearance < 45 ml/min have not been studied in sufficient numbers when treated with pemetrexed, as contained in **PEMTORI IV**. Therefore, the use of **PEMTORI IV** in these patients is not recommended (see section 4.2).

Non-steroidal anti-inflammatory drugs (NSAIDs) with short-elimination half-lives, such as ibuprofen and acetylsalicylic acid, should be avoided for at least 2 days prior to, on the day of, and at least 2 days after

administration of **PEMTORI IV** in those patients with mild to moderate renal insufficiency (creatinine clearance from 45 – 79 ml/min).

All patients eligible for **PEMTORI IV** 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 **PEMTORI IV** 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. The majority of 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 have also been 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. The administration of pemetrexed in solid tumour patients with normal renal function and with stable third space fluid demonstrates no difference in pemetrexed dose normalised plasma concentrations or clearance, compared to patients without third space fluid collections. Thus, drainage of third space fluid collection prior to administration of **PEMTORI IV** in patients with normal renal function should be considered, but may not be necessary.

Serious cardiovascular events, including myocardial infarction and cerebrovascular events, have been reported rarely when pemetrexed, as contained in **PEMTORI IV** is given in combination with another cytotoxic medicine, or in patients with cardiovascular risk factors (see section 4.8).

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 treatment.

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

Pemetrexed can have genetically damaging effects. Sexually mature males are advised not to father a child during, and up to 6 months after the treatment. 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 pemetrexed, pregnancy should be avoided (see section 4.6).

Radiation pneumonitis has been reported in some 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 medicines.
Cases of radiation recall have been reported in patients who received radiotherapy weeks or years previously.

4.5 Interaction with other medicines and other forms of interaction

Pemetrexed as in **PEMTORI IV** is primarily eliminated unchanged renally by tubular secretion and to a lesser extent by glomerular filtration. Pemetrexed is actively secreted by OAT3 (organic anion transporter 3). Concomitant administration of nephrotoxic medicines, (e.g. aminoglycoside, loop diuretics, platinum compounds, cyclosporin), 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 medicines that are tubularly secreted (e.g. probenecid, penicillin) could potentially result in delayed clearance of pemetrexed. Caution should be made during concomitant use of **PEMTORI IV** with these medicines. If necessary, creatinine clearance should be closely monitored.
Although NSAIDS in moderate doses can be administered with **PEMTORI IV** in patients with normal renal function (creatinine clearance ≥ 80 ml/min), caution should be used when administering NSAIDS concurrently with **PEMTORI IV** to patients with mild to moderate renal insufficiency (creatinine clearance 45 – 79 ml/min), the concomitant administration of pemetrexed with NSAIDs (e.g. ibuprofen) 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 between pemetrexed as in **PEMTORI IV** and NSAIDs with longer half-lives (e.g. piroxicam) patients with mild to moderate renal insufficiency taking these NSAIDs should interrupt dosing for at least 5 days before, on the day of, and at least 2 days after **PEMTORI IV** administration. If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression and gastrointestinal toxicity.
Acetylsalicylic acid, administered in low to moderate doses (325 mg orally every 6 hours) does not affect the pharmacokinetics of pemetrexed as in **PEMTORI IV**.
The pharmacokinetics of pemetrexed as in **PEMTORI IV** are not influenced by concurrently administered cisplatin or carboplatin. Similarly, the pharmacokinetics of total platinum are unaltered by **PEMTORI IV** pemetrexed. Oral folic acid and intramuscular vitamin B12 supplementation do not affect the pharmacokinetics of pemetrexed as in **PEMTORI IV**.

Pemetrexed as in **PEMTORI IV** undergoes limited hepatic metabolism and is not expected to cause clinically significant inhibition of the metabolic clearance of medicines 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 such as **PEMTORI IV** require increased frequency of INR (International Normalised Ratio) monitoring, if it is decided to treat the patient with oral anticoagulants.

Concomitant use with Yellow fever vaccine, due to the risk of fatal generalised vaccinale disease is contraindicated (see section 4.3).

Concomitant use of live attenuated vaccines (except yellow fever, for which concomitant use is contraindicated), due to the risk of systemic, possibly fatal, disease is not recommended. 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

Women of childbearing potential / Contraception in males and females

PEMTORI IV therapy may cause teratogenicity and other reproductive adverse events due to its genotoxic nature. In males, **PEMTORI IV** may cause DNA damage in the sperm, potentially resulting in adverse events in the embryo or foetus of a female sexual partner. In females, **PEMTORI IV** may directly affect the embryo or foetus; or may cause DNA damage in the oocytes.

Male patients should be advised to use highly effective contraception while receiving treatment with **PEMTORI IV**, until the end of relevant systemic exposure to this product, including its potential genotoxic metabolites (i.e., five half-lives after the last dose, which is 40 days) plus 90 days (i.e., 60 - 75 days for sperm production plus 10 - 14 days for the transport to the epididymis) giving 130 days (4 months and 10 days) after the last dose.

Women of childbearing potential, that is female patients using **PEMTORI IV** and female sexual partners of male patients receiving **PEMTORI IV**, should be advised to use highly effective contraception until the end of relevant systemic exposure to **PEMTORI IV**, including its potential genotoxic metabolites (i.e., five half-lives after the last dose, which is 40 days) plus 6 months (which covers the growth and maturation phase of folliculogenesis). This gives a total of 7 months and 10 days.

Pregnancy

Safety in pregnancy has not been established.

There is no data on the use of pemetrexed as in **PEMTORI IV** in pregnant women. Animal studies have shown reproductive toxicity such as birth defects and other defects on the development of the foetus, the course of gestation and peri- and post-development. The potential risk for humans is unknown. Therefore, the use of **PEMTORI IV** 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 **PEMTORI IV**.

Breastfeeding

Safety during lactation has not been established.

It is not known whether pemetrexed is excreted in human milk. Therefore, breast feeding is not recommended during **PEMTORI IV** therapy.

Fertility

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

4.7 Effects on ability to drive and use machines:

PEMTORI IV may cause fatigue. Patients should be cautioned against driving or operating machinery.

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. Rarely seen events include Stevens-Johnson syndrome and Toxic epidermal necrolysis.

Tabulated list of adverse effects

In combination with cisplatin supplemented with folic acid and vitamin B12 (malignant pleural mesothelioma):

System Organ Class	Frequency	Side effects
Infections and Infestations	Frequent	Infection
Blood and lymphatic system disorders	Frequent	Neutrophils/granulocytes decreased, leukocytes decreased, haemoglobin decreased, platelets decreased, 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, stomatitis/pharyngitis, anorexia, diarrhoea, constipation, dyspepsia
Hepato-biliary disorders	Frequent	Increased AST, ALT and GGT
Skin and subcutaneous tissue disorders	Frequent	Rash, alopecia, urticaria

System Organ Class	Frequency	Side effects
Renal and urinary disorders	Frequent	Serum creatinine elevation, creatinine clearance decreased, renal failure
General disorders and administrative site conditions	Frequent	Fatigue, pyrexia, chest pain

In combination with cisplatin, supplemented with folic acid and vitamin B_{12} (Non-small lung cell cancer):

System Organ Class	Frequency	Side effects
Infections and Infestations:	Frequent	Infection
Blood and lymphatic system disorders:	Frequent	Neutrophils/granulocytes decreased, leukocytes decreased, haemoglobin decreased, platelets decreased, febrile neutropenia
Metabolism and nutrition disorders:	Frequent	Dehydration
Nervous system disorders:	Frequent Less frequent	Neuropathy-sensory, taste disturbance Motor neuropathy
Eye disorders:	Frequent	Conjunctivitis
Cardiac disorders:	Less frequent	Chest pain, dysrhythmia
Gastrointestinal disorders:	Frequent	Nausea, vomiting, anorexia, constipation, stomatitis/pharyngitis,

		diarrhoea without colostomy, dyspepsia/heartburn
Hepato-biliary disorders:	Frequent	AST and ALT increased, GGT increase
Skin and subcutaneous tissue disorders:	Frequent	Alopecia, rash/desquamation
Renal and urinary disorders:	Frequent	Creatinine clearance decreased, renal failure
General disorders and administrative site conditions:	Frequent	Fatigue, pyrexia

Single medicine PEMTORI IV supplemented with folic acid and vitamin B_{12} after prior chemotherapy:

System Organ Class	Frequency	Side effects
Infections and Infestations:	Frequent	Infection, sepsis
Blood and lymphatic system disorders:	Frequent Less frequent	Haemoglobin decreased, leucocytes decreased, neutrophils/granulocytes decreased, platelets decreased, febrile neutropenia, infection without neutropenia, bone marrow depression Pancytopenia
Immune system disorders:	Frequent Frequency unknown	Allergic reaction/hypersensitivity

System Organ Class	Frequency	Side effects
		Anaphylactic shock, immune-mediated haemolytic anaemia
Nervous system disorders:	Frequent Less frequent	Sensory neuropathy, motor neuropathy, dizziness Transient ischaemic attack, cerebrovascular accident
Eye disorders	Frequent	Ocular surface disease, conjunctivitis, increased lacrimation
Cardiac disorders:	Less frequent	Supraventricular dysrhythmias, myocardial infarction, angina pectoris
Vascular disorders:	Less frequent	Peripheral ischeamia, pulmonary embolism
Respiratory, thoracic and mediastinal disorders	Less frequent	Oesophagitis/ radiation oesophagitis, radiation pneumonitis, interstitial pneumonitis with respiratory insufficiency
Gastrointestinal disorders:	Frequent Less frequent	Nausea, anorexia, vomiting, stomatitis/mucositis, diarrhoea, constipation, AST (SGOT), abdominal pain, dehydration Colitis (including intestinal and rectal bleeding, sometimes fatal,

System Organ Class	Frequency	Side effects
		intestinal perforation, intestinal necrosis and typhlitis)
Hepato-biliary disorders:	Frequent Less frequent	ALT (SGPT) increased Hepatitis
Skin and subcutaneous tissue disorders:	Frequent Less frequent Frequency unknown	Rash/desquamation, pruritus, alopecia, erythema multiforme, hyperpigmentation Bullous conditions including Stevens-Johnson syndrome and toxic epidermal necrolysis Erythematous oedema, acute bacterial dermo-hypodermitis, pseudocellulitis, dermatitis
Renal and urinary disorders:	Frequent Less frequent	Increased and decreased creatinine, decreased glomerular filtration rate Acute renal failure, nephrogenic diabetes insipidus and renal tubular necrosis
General disorders and administrative site conditions:	Frequent	Fatigue, fever, pain, oedema
Injury and poisoning:	Frequency unknown	Radiation recall

Single medicine PEMTORI IV supplemented with folic acid and vitamin B12 for adenocarcinoma of lung maintenance:

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 infection without neutropenia, bone marrow depression Pancytopenia
Immune system disorders:	Less frequent Frequency unknown	Allergic reactions/hypersensitivity Anaphylactic shock, immune-mediated haemolytic anaemia
Nervous system disorders:	Frequent Less frequent	Sensory neuropathy, motor neuropathy, dizziness Transient ischaemic attack, cerebrovascular accident
Eye disorders:	Frequent	Ocular surface disease (including conjunctivitis), increased lacrimation
Cardiac disorders:	Less frequent	Supraventricular dysrhythmia, myocardial infarction, angina pectoris
Vascular disorders:	Less frequent	Peripheral ischeamia, pulmonary embolism

System Organ Class	Frequency	Side effects
Respiratory, thoracic and mediastinal disorders	Less frequent	Radiation pneumonitis, interstitial pneumonitis with respiratory insufficiency
Gastrointestinal disorders:	Frequent	Nausea, anorexia, vomiting, mucositis/stomatitis, diarrhoea, constipation, dehydration
	Less frequent	Colitis (including intestinal and rectal bleeding, sometimes fatal, intestinal perforation, intestinal necrosis and typhlitis), oesophagitis/ radiation oesophagitis
Hepato-biliary disorders:	Frequent	ALT (SGPT), AST (SGOT) increased
	Less frequent	Hepatitis
Skin and subcutaneous tissue disorders:	Frequent	Rash/desquamation, alopecia, pruritus/itching, erythema multiforme, hyperpigmentation
	Less frequent	Bullous conditions including Stevens-Johnson syndrome and toxic epidermal necrolysis
	Frequency unknown	Erythematous oedema, acute bacterial dermo-hypodermitis, pseudocellulitis, dermatitis

System Organ Class	Frequency	Side effects
Renal and urinary disorders:	Frequent Less frequent	Decreased creatinine clearance, increased creatinine, decreased glomerular filtration rate Acute renal failure, nephrogenic diabetes insipidus and renal tubular necrosis
General disorders and administrative site conditions:	Frequent	Fatigue, fever (in the absence of neutropenia), pain oedema
Injury and poisoning:	Frequency unknown	Radiation recall

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 providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Signs and symptoms:

Reported symptoms of overdose include neutropenia, anaemia, thrombocytopenia, mucositis, sensory neuropathy 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.

Management of overdose:

In the event of suspected overdose, patients should be monitored with blood counts and should receive supportive therapy as necessary. The use of leucovorin (calcium folinate / folinic acid) in the management of **PEMTORI IV** overdosage should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Folic acid analogues

ATC code: L01BA04

Pharmacological classification: A 26: Cytostatic agents

Pemetrexed is a multi-target anti-cancer anti-folate medicine that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell-replication.

In vitro studies show that pemetrexed behaves as a multi-target anti-folate by inhibiting thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyltransferase (GARFT); the 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 folyl polyglutamate 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

The pharmacokinetics of pemetrexed are consistent over multiple treatment cycles.

Absorption:

Pemetrexed total systemic exposure (AUC) and maximum plasma concentration increase proportionally with dose.

Distribution:

In cancer patients with a variety of solid tumours, pemetrexed has a steady-state volume of distribution of 16,1 litres.

Biotransformation:

Pemetrexed is 81 % bound to plasma proteins; binding is not notably affected by varying degrees of renal impairment. Pemetrexed undergoes limited hepatic metabolism.

Elimination:

Pemetrexed is primarily eliminated in the urine, with 70 % to 90 % recovered unchanged in the 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 %.

5.3 Preclinical safety data

Administration of pemetrexed 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. In a study conducted in beagle dog by intravenous bolus injection for 9 months, testicular findings (degeneration/necrosis of the seminiferous epithelium) have been observed. This suggests that pemetrexed may impair male fertility. 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

Hydrochloric acid (pH adjustment)

Mannitol

Sodium hydroxide (pH adjustment)

6.2 Incompatibilities

Pemetrexed is physically incompatible with diluents containing calcium, including lactated Ringer's injection and Ringer's injection. In the absence of other compatibility studies

PEMTORI IV must not be mixed with other medicine.

PEMTORI IV should ONLY be reconstituted and diluted with 0,9 % sodium chloride solution for injection, without preservative (see preparation instructions above).

PEMTORI IV is compatible with standard polyvinyl chloride administration sets and intravenous solution bags. **PEMTORI IV** is physically incompatible with lactated Ringer’s Injection and Ringer’s Injection.

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

6.3 Shelf life

Unopened vial: 24 months.

After dilution in Infusion media: 24 hours at 2 °C – 8 °C.

6.4 Special precautions for storage

Powder: Store at or below 25 °C.

Keep the vial in the carton until required for use.

Reconstituted solution: Store between 2 – 8 °C (in a refrigerator) and use within 24 hours. Discard any unused portion. See section 6.6

6.5 Nature and contents of container

PEMTORI IV 100: Clear 10 ml glass vial with grey rubber plug, aluminium seal with black flip off cap. Each vial is placed in an outer carton.

PEMTORI IV 500: Clear 50 ml glass vial with grey rubber plug, aluminium seal with black flip off cap. Each vial is placed in an outer carton.

6.6 Special precautions for disposal and other handling of the product

The powder for solution for infusion is for single use only.

PEMTORI IV solution must be prepared as follows:

1. Use appropriate aseptic techniques during the reconstitution and further dilution of **PEMTORI IV** for intravenous administration.
2. Calculate the dose and number of **PEMTORI IV** vials needed. The vial contains an excess of **PEMTORI IV** to facilitate delivery of the label amount.
3. Prior to administration, each vial of **PEMTORI IV 100** or **PEMTORI IV 500** must be reconstituted with 4,2 ml or 20 ml, respectively, of 0,9 % sodium chloride solution for injection, without preservative, resulting in a solution with a concentration of approximately 25 mg/ml pemetrexed. Slowly add the 0,9 % sodium chloride solution for injection, without preservative, to the vial and gently swirl until the powder is completely dissolved.
4. **The reconstituted PEMTORI IV solution must be further diluted with 0,9 % sodium chloride solution for injection, without preservative, prior to intravenous infusion.** Transfer the reconstituted **PEMTORI IV** solution from the vial into an IV bag, and further dilute to 100 ml with the same diluent. Gently mix to obtain a homogeneous solution.

5. **PEMTORI IV** contains no antibacterial preservative. For the reconstituted solution, chemical and physical in-use stability has been demonstrated for 24 hours at refrigerated temperatures. From a microbiological point of view, **PEMTORI IV** 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. **PEMTORI IV** should be inspected visually for particulate matter and discolouration prior to administration.
7. **PEMTORI IV** solution should then be administered by intravenous infusion over 10 minutes.
8. Procedures for proper handling and disposal should be observed. Care should be exercised in the handling and preparation of infusion solutions of **PEMTORI IV**.

   PEMTORI IV powder for solution for infusion is for single use only. Any unused contents of the vial should be disposed of in accordance with local requirement.

Preparation and administration precautions:

As with other potentially toxic anticancer medicines, 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 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.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

MC Pharma (Pty) Ltd

62 Constantia Avenue

Mnandi

0157

South Africa

8. REGISTRATION NUMBER(S)

PEMTORI IV 100 mg: 50/26/0868

PEMTORI IV 500 mg: 50/26/0869

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 March 2021

10. DATE OF REVISION OF THE TEXT

25 March 2025