**PROFESSIONAL INFORMATION**

**SCHEDULING STATUS**

**S4**

## 1. NAME OF THE MEDICINE

**PEMETREXED 500 mg/20 mL FRESENIUS** 25 mg/mL concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL contains 25 mg pemetrexed as pemetrexed diacid.

Sugar free.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

PEMETREXED 500 mg/20 mL FRESENIUS is a colourless to slightly yellowish or yellow-greenish solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

PEMETREXED 500 mg/20 mL FRESENIUS is indicated for the treatment of patients with malignant pleural mesothelioma in combination with cisplatin.

PEMETREXED 500 mg/20 mL FRESENIUS 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.

PEMETREXED 500 mg/20 mL FRESENIUS is indicated as monotherapy for the treatment of patients with locally advanced or metastatic adenocarcinoma of the lung after prior chemotherapy.

PEMETREXED 500 mg/20 mL FRESENIUS 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

PEMETREXED 500 mg/20 mL FRESENIUS should only be administered under the supervision of a medical practitioner qualified in the use of anti-cancer chemotherapy.

**Posology**

***Malignant pleural mesothelioma:***

Combination use with cisplatin:

Adults: In patients treated for malignant pleural mesothelioma, the recommended dose of PEMETREXED 500 mg/20 mL FRESENIUS 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 PEMETREXED 500 mg/20 mL FRESENIUS 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 PEMETREXED 500 mg/20 mL FRESENIUS 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 PEMETREXED 500 mg/20 mL FRESENIUS 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 PEMETREXED 500 mg/20 mL FRESENIUS 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 PEMETREXED 500 mg/20 mL FRESENIUS 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 PEMETREXED 500 mg/20 mL FRESENIUS should also receive vitamin supplementation (see section 4.4). Patients must take oral folic acid or multivitamin containing folic acid (350 to 1 000 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 PEMETREXED 500 mg/20 mL FRESENIUS, and dosing should continue during the full course of therapy and for 21 days after the last dose of PEMETREXED 500 mg/20 mL FRESENIUS. Patients must also receive an intramuscular injection of vitamin $B_{12}$ (1 000 mcg) in the week preceding the first dose of PEMETREXED 500 mg/20 mL FRESENIUS and every 3 cycles thereafter.

***Monitoring:***

Patients receiving PEMETREXED 500 mg/20 mL FRESENIUS 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 ≥1 500 cells/$mm^3$ and platelets should be ≥100 000 cells/$mm^3$ prior to the start of each cycle.

***Dose adjustments:***

Dose adjustments at the start of a subsequent cycle should be based on nadir haematologic counts or maximum non-haematologic toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery, patients may be retreated using the guidelines in Tables 1, 2 and 3,

which are applicable for PEMETREXED 500 mg/20 mL FRESENIUS used as a single medicine or in combination with cisplatin.

| **TABLE 1: DOSE MODIFICATION TABLE FOR PEMETREXED 500 mg/20 mL FRESENIUS (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 PEMETREXED 500 mg/20 mL FRESENIUS and cisplatin |
| Nadir platelets ≤50 000/mm$^3$ without bleeding regardless of nadir ANC | 50 % of previous dose PEMETREXED 500 mg/20 mL FRESENIUS and cisplatin |
| Nadir platelets ≤50 000/mm$^3$ with bleeding[a] regardless of nadir ANC | 50 % of previous dose PEMETREXED 500 mg/20 mL FRESENIUS 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.

| **TABLE 2: DOSE MODIFICATION TABLE FOR PEMETREXED 500 mg/20 mL FRESENIUS (AS SINGLE MEDICINE OR IN COMBINATION) AND CISPLATIN: NON-HAEMATOLOGIC TOXICITIES [a,b]** | | |
|---|---|---|
| | **Dose of PEMETREXED 500 mg/20 mL FRESENIUS ($mg/m^2$)** | **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)<br>[b] Excluding neurotoxicity | | |

In the event of neurotoxicity, the recommended dose adjustment for PEMETREXED 500 mg/20 mL FRESENIUS 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 PEMETREXED 500 mg/20 mL FRESENIUS** |
|---|

| **(AS A SINGLE MEDICINE OR IN COMBINATION) AND CISPLATIN: NEUROTOXICITY** | | |
|---|---|---|
| **CTC* Grade** | **Dose of PEMETREXED 500 mg/20 mL FRESENIUS (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) | | |

Treatment with PEMETREXED 500 mg/20 mL FRESENIUS 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:* No dose reductions other than those recommended for all patients are necessary (see section 4.8).

*Paediatrics:* PEMETREXED 500 mg/20 mL FRESENIUS is not recommended for use in patients under 18 years of age, as safety and efficacy have not been established in this group of patients.

*Patients with renal impairment* (Standard Cockcroft and Gault formula or Glomerular Filtration Rate measured by Tc99m-DPTA serum clearance method): PEMETREXED 500 mg/20 mL FRESENIUS is primarily eliminated unchanged by renal excretion. 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 500 mg/20 mL FRESENIUS in

patients with creatinine clearance below 45 mL/min; therefore, the use of PEMETREXED 500 mg/20 mL FRESENIUS is not recommended (see section 4.4).

*Patients with hepatic impairment:* No relationships between aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/ serum glutamic pyruvic transaminase (SGPT), or total bilirubin and PEMETREXED 500 mg/20 mL FRESENIUS 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**

PEMETREXED 500 mg/20 mL FRESENIUS is for intravenous infusion.

PEMETREXED 500 mg/20 mL FRESENIUS must be diluted prior to administration. For information on instructions for dilution, see section 6.6.

*Appearance of the diluted solution:*

The diluted product is a clear, colourless or yellow-greenish solution free from visible particles.

PEMETREXED 500 mg/20 mL FRESENIUS should be inspected visually for particulate matter and discolouration prior to administration.

PEMETREXED 500 mg/20 mL FRESENIUS solution should then be administered by intravenous infusion over 10 minutes.

**PEMETREXED 500 mg/20 mL FRESENIUS should ONLY be diluted with 0,9 % sodium chloride injection or 5 % glucose intravenous infusion** (also see section 6.6 for more information).

PEMETREXED 500 mg/20 mL FRESENIUS is physically incompatible with diluents containing calcium, including lactated Ringer's Injection and Ringer's Injection (see section 6.2).

Co-administration of PEMETREXED 500 mg/20 mL FRESENIUS with other medicines and diluents has not been studied and therefore is not recommended.

### 4.3 Contraindications

- Hypersensitivity to pemetrexed, or to any of the excipients (see section 6.1)
- Concomitant yellow fever vaccine (see section 4.5).

### 4.4 Special warnings and precautions for use

PEMETREXED 500 mg/20 mL FRESENIUS can suppress bone marrow function as manifested by neutropenia, thrombocytopenia, anaemia or pancytopenia (see sections 4.4, 4.8). Myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for myelosuppression during therapy and PEMETREXED 500 mg/20 mL FRESENIUS should not be given to patients until absolute neutrophil count (ANC) returns to ≥1 500 cells/$mm^3$ and platelet count returns to ≥100 000 cells/$mm^3$. Dose reductions for subsequent cycles are based on nadir ANC, platelet count and maximum non-haematologic toxicity seen from the previous cycle (see section 4.2).

Less toxicity and reduction in Grade 3/4 haematologic and non-haematologic toxicities such as neutropenia, febrile neutropenia and infection with Grade 3/4

neutropenia were reported when pre-treatment with folic acid and vitamin $B_{12}$ was administered. Therefore, all patients treated with PEMETREXED 500 mg/20 mL FRESENIUS 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 has been studied with creatinine clearance of <45 mL/min. Therefore, the use of PEMETREXED 500 mg/20 mL FRESENIUS 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) with short-elimination half-lives for at least 2 days prior to, on the day of, and at least 2 days after administration of PEMETREXED 500 mg/20 mL FRESENIUS. All patients eligible for PEMETREXED 500 mg/20 mL FRESENIUS 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 500 mg/20 mL FRESENIUS 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 500 mg/20 mL FRESENIUS is not fully defined. Drainage of third space fluid collection prior to PEMETREXED 500 mg/20 mL FRESENIUS treatment in patients with normal renal function should be considered but may not be necessary.

Due to the gastrointestinal toxicity of PEMETREXED 500 mg/20 mL FRESENIUS 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.

Serious cardiovascular events, including myocardial infarction and cerebrovascular events have been less frequently 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 common in cancer patients. As a result, concomitant use of live attenuated vaccines is not recommended (see sections 4.3, 4.5).

PEMETREXED 500 mg/20 mL FRESENIUS 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 500 mg/20 mL FRESENIUS 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 500 mg/20 mL FRESENIUS (see section 4.6).

Cases of radiation pneumonitis have been reported in patients treated with radiation either prior, during or subsequent to their pemetrexed therapy. Particular attention should be paid to these patients and caution exercised with use of other radiosensitising 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 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. Concomitant administration of substances that are tubularly secreted (e.g. probenecid, penicillin) could potentially result in delayed clearance of pemetrexed.

Although NSAIDs in moderate doses can be administered with PEMETREXED 500 mg/20 mL FRESENIUS in patients with normal renal function (creatinine clearance ≥80 mL/min), caution should be used when administering NSAIDs concurrently with PEMETREXED 500 mg/20 mL FRESENIUS to patients with renal insufficiency (creatinine clearance 45 – 79 mL/min).

A decrease was shown in pemetrexed clearance following co-administration of ibuprofen. It is recommended that patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives at least 2 days prior to, on the day of, and at least 2 days after administration of PEMETREXED 500 mg/20 mL FRESENIUS.

In the absence of data regarding potential interaction between PEMETREXED 500 mg/20 mL FRESENIUS and NSAIDs with longer half-lives, such as piroxicam or rofecoxib 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 PEMETREXED 500 mg/20 mL FRESENIUS 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 500 mg/20 mL FRESENIUS.

The pharmacokinetics of pemetrexed are not influenced by concurrently administered cisplatin or carboplatin. Similarly, the pharmacokinetics of total

platinum are unaltered by pemetrexed. Oral folic acid and intramuscular vitamin $B_{12}$ supplementation do not affect the pharmacokinetics of pemetrexed.

PEMETREXED 500 mg/20 mL FRESENIUS undergoes limited hepatic metabolism. PEMETREXED 500 mg/20 mL FRESENIUS would not be predicted 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 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

**Women of childbearing potential / Contraception in males and females**

Women of childbearing potential must use effective contraception during treatment with PEMETREXED 500 mg/20 mL FRESENIUS. Woman should be advised to avoid becoming pregnant while being treated with PEMETREXED 500 mg/20 mL FRESENIUS, due to the potential hazard to the foetus.

PEMETREXED 500 mg/20 mL FRESENIUS 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 500 mg/20 mL FRESENIUS 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 PEMETREXED 500 mg/20 mL FRESENIUS should be avoided during pregnancy due to the potential hazard to the foetus.

**Breastfeeding**

It is not known whether PEMETREXED 500 mg/20 mL FRESENIUS is excreted in human milk. Therefore, it is not recommended that breastfeeding be continued during PEMETREXED 500 mg/20 mL FRESENIUS therapy.

**Fertility**

Owing to the possibility of PEMETREXED 500 mg/20 mL FRESENIUS treatment causing irreversible infertility, men are advised to seek counselling on sperm storage before starting treatment.

### 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, it has been reported that PEMETREXED 500 mg/20 mL FRESENIUS may cause fatigue, eye disorders or neuropathy. Therefore, patients should be cautioned against driving or operating machinery.

- **4.8 Undesirable effects**

*a) Summary of the safety profile*

The most frequently reported undesirable effects related to PEMETREXED 500 mg/20 mL FRESENIUS, 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 seen events include Stevens-Johnson syndrome and toxic epidermal necrolysis.

*b) Tabulated summary of adverse reactions*

| System Organ Class | Frequent | Less frequent |
|---|---|---|

| | | |
|---|---|---|
| Infections and infestations | Infection[a], pharyngitis, sepsis[b] | Dermo-hypodermitis |
| Blood and lymphatic system disorders | Neutropenia, leukopenia, decreased haemoglobin, febrile neutropenia, decreased platelet count | Pancytopenia, autoimmune haemolytic anaemia |
| Immune system disorders | Hypersensitivity | Anaphylactic shock |
| Metabolism and nutrition disorders | Dehydration | |
| Nervous system disorders | Taste disorder, peripheral motor neuropathy, sensory neuropathy<br>dizziness | Cerebrovascular accident, ischaemia stroke, intracranial haemorrhage |
| Eye disorders | Conjunctivitis, dry eye, increased lacrimation, keratoconjunctivitis sicca, eyelid oedema, ocular surface disease | |
| Cardiac disorders | Cardiac failure, dysrhythmia | Angina, myocardial infarction, coronary artery disease, supraventricular dysrhythmia |
| Vascular disorders | | Peripheral ischaemia[c] |

| | | |
|---|---|---|
| Gastrointestinal disorders | Stomatitis, anorexia, vomiting, diarrhoea, nausea, dyspepsia, constipation, abdominal pain, mucositis | Rectal haemorrhage, gastrointestinal haemorrhage, intestinal perforation |
| Hepatobiliary disorders | Increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST) | Hepatitis |
| Skin and subcutaneous tissue disorders | Rash, skin exfoliation, hyperpigmentation, pruritus, erythema multiforme, alopecia, urticaria, desquamation | Erythema, pemphigoid, acquired epidermolysis bullosa, erythematous oedema[e], pseudocellulitis, dermatitis, eczema, prurigo |
| Renal and urinary disorders | Decreased creatinine clearance, increased blood creatinine[d], renal failure, decreased glomerular filtration rate | Nephrogenic diabetes insipidus, renal tubular necrosis |
| General disorders and administration site conditions | Fatigue, pyrexia, pain, chest pain, mucosal inflammation | |

| | | |
|---|---|---|
| Investigations | Increased gamma-glutamyl transferase | |
| Injury, poisoning and procedural complications | | Radiation oesophagitis, radiation pneumonitis |

[a] with and without neutropenia

[b] in some cases fatal

[c] sometimes leading to extremity necrosis

[d] seen only in combination with cisplatin

[e] mainly of the lower limbs

**Post-Marketing data:**

| **System organ class** | **Less frequent** |
|---|---|
| **Respiratory, thoracic and mediastinal disorders** | Interstitial pneumonitis<br>Pulmonary embolism |
| **Gastrointestinal disorders** | Colitis |
| **Skin and subcutaneous tissue disorders** | Bullous conditions<br>Stevens-Johnson syndrome[1]<br>Toxic epidermal necrolysis[2] |
| **General disorders and administrative site conditions** | Oedema |
| **Injury, poisoning and procedural complications** | Radial recall[3] |

[1, 2] Were fatal in some cases

[3] In patients who previously received radiotherapy

*c) Description of selected adverse reactions*

Sepsis which in some cases was fatal occurred in approximately 1 % of patients.

Nephrogenic diabetes insipidus and renal tubular necrosis were reported with PEMETREXED 500 mg/20 mL FRESENIUS alone or with other chemotherapeutic medicines. The frequency of these events is unknown and most of these events resolved after PEMETREXED 500 mg/20 mL FRESENIUS withdrawal (see section 4.4).

Serious cardiovascular events, including myocardial infarction and cerebrovascular events have been less frequently reported with PEMETREXED 500 mg/20 mL FRESENIUS, usually when given in combination with another cytotoxic medicine (see section 4.4).

*d) Special populations*

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 (see section 4.2).

*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.

Healthcare providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

### 4.9 Overdose

**Symptoms**

Reported symptoms of overdose include neutropenia, anaemia, thrombocytopenia 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 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 PEMETREXED 500 mg/20 mL FRESENIUS overdosage should be considered.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Category and Class: A 26: Cytostatic agents

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, antineoplastic agents, antimetabolites, folic acid analogues

ATC code: L01BA04

*Mechanism of action*

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

*Pharmacodynamic effects*

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 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**

*Distribution*

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

*Biotransformation*

Pemetrexed undergoes limited hepatic metabolism.

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

*Elimination*

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).

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.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Hydroxypropylbetadex

Hydrochloric acid (for pH adjustment)

Trometamol (for pH adjustment)

Water for injection

## 6.2 Incompatibilities

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

PEMETREXED 500 mg/20 mL FRESENIUS is physically incompatible with diluents containing calcium, including lactated Ringer's Injection and Ringer's Injection (see section 4.2).

Co-administration of PEMETREXED 500 mg/20 mL FRESENIUS with other medicines and diluents has not been studied and therefore is not recommended.

## 6.3 Shelf life

Unopened vial

24 months.

Diluted solution

PEMETREXED 500 mg/20 mL FRESENIUS contains no antibacterial preservative. For the diluted solution, chemical and physical in-use stability has been demonstrated for 21 days when stored between 2 °C and 8 °C and 7 days when stored at or below 25 °C.

From a microbiological point of view, the product 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 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

## 6.4 Special precautions for storage

Store at or below 25 °C.

For storage conditions after dilution, see section 6.3.

### 6.5 Nature and contents of container

20 mL concentrate in a 30 mL Type-I tubular clear, colourless glass vial, closed with 20 mm grey, flurotec, chlorobutyl rubber stopper/ or 20 mm bromobutyl rubber stopper and sealed with aluminium flip off seal.

Pack of 1 vial in a carton.

### 6.6 Special precautions for disposal and other handling

PEMETREXED 500 mg/20 mL FRESENIUS should only be administered under the supervision of a medical practitioner qualified in the use of anti-cancer chemotherapy.

PEMETREXED 500 mg/20 mL FRESENIUS solution must be diluted with 0,9 % sodium chloride injection or 5 % glucose intravenous infusion prior to intravenous infusion. Dilute the appropriate volume of PEMETREXED 500 mg/20 mL FRESENIUS solution to 100 mL of 0,9 % sodium chloride injection or 100 mL of 5 % glucose intravenous infusion. The bag should be inverted gently to mix the solution to obtain a homogeneous solution.

The diluted product is a clear, colourless or yellow-greenish solution free from visible particles.

PEMETREXED 500 mg/20 mL FRESENIUS infusion solutions prepared as directed above are compatible with polyvinyl chloride and polyolefin lined administration sets and infusion bags.

PEMETREXED 500 mg/20 mL FRESENIUS solutions are for single use only. Any unused contents of the vial should be discarded.

Preparation and administration precautions

As with other potentially toxic anticancer medicines, care should be exercised in the handling and preparation of PEMETREXED 500 mg/20 mL FRESENIUS infusion solutions. The use of gloves is recommended. If a PEMETREXED 500 mg/20 mL FRESENIUS solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If PEMETREXED 500 mg/20 mL FRESENIUS solutions contact the mucous membranes, flush thoroughly with water. PEMETREXED 500 mg/20 mL FRESENIUS is not a vesicant. There is no specific antidote for extravasation of PEMETREXED 500 mg/20 mL FRESENIUS. There have been few reported cases of PEMETREXED 500 mg/20 mL FRESENIUS extravasation, which were not assessed as serious. Extravasation should be managed by standard practice as with other non-vesicants.

## 7 HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Limited

Stand 7, Growthpoint Business Park

162 Tonetti Street

Halfway House extension 7, Midrand

Gauteng

1685

## 8 REGISTRATION NUMBER

56/26/0954

## 9 DATE OF FIRST AUTHORISATION

08 April 2025

## 10 DATE OF REVISION OF TEXT