เอกสารกำกับยาภาษาอังกฤษ

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PEMETREXED 100 EURODRUG 100 mg powder for concentrate for solution for infusion

PEMETREXED 500 EURODRUG 500 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PEMETREXED 100 EURODRUG 100 mg powder for concentrate for solution for infusion

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

Excipient with known effect

Each vial contains approximately 11 mg sodium.

PEMETREXED 500 EURODRUG 500 mg powder for concentrate for solution for infusion

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

Excipient with known effect

Each vial contains approximately 54 mg sodium.

After reconstitution (see section 6.6), each vial contains 25 mg/ml of pemetrexed.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to light yellow lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Malignant pleural mesothelioma

Pemetrexed in combination with cisplatin is indicated for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma.

Non-small cell lung cancer

Pemetrexed in combination with cisplatin is indicated for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology (see section 5.1).

Pemetrexed is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy (see section 5.1).

Pemetrexed is indicated as monotherapy for the second line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology (see section 5.1).

4.2 Posology and method of administration

Posology

Pemetrexed must only be administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy.

Pemetrexed in combination with cisplatin

The recommended dose of pemetrexed is 500 mg/m^2 of body surface area (BSA) 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 BSA infused over two hours approximately 30 minutes after completion of the pemetrexed infusion on the first day of each 21-day cycle. Patients must receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving cisplatin (see also cisplatin Summary of Product Characteristics for specific dosing advice).

Pemetrexed as single agent

In patients treated for non-small cell lung cancer after prior chemotherapy, the recommended dose of pemetrexed is 500 mg/m^2 BSA administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

Pre-medication 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 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 must also receive vitamin supplementation (see section 4.4). Patients must take oral folic acid or a multivitamin containing folic acid (350 to 1000 micrograms) on a daily basis. At least five doses of folic acid must be taken during the seven days preceding the first dose of pemetrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients must also receive an intramuscular injection of vitamin B_{12} (1000 micrograms) in the week preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B_{12} injections may be given on the same day as pemetrexed.

Monitoring

Patients receiving pemetrexed should be monitored before each dose with a complete blood count, including a differential white cell count (WCC) and platelet count. Prior to each chemotherapy administration blood chemistry tests should be collected to evaluate renal and hepatic function. Before the start of any cycle of chemotherapy, patients are required to have the following: absolute neutrophil count (ANC) should be ≥1500 cells/mm^3 and platelets should be ≥100,000 cells/mm^3.

Creatinine clearance should be ≥45 ml/min.

The total bilirubin should be ≤1.5 times upper limit of normal. Alkaline phosphatase (AP), aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT) should be ≤3 times upper limit of normal. Alkaline phosphatase, AST and ALT ≤5 times upper limit of normal is acceptable if liver has tumour involvement.

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 should be retreated using the guidelines in Tables 1, 2 and 3, which are applicable for pemetrexed used as a single agent or in combination with cisplatin.

Table 1 Dose modification table for pemetrexed (as single agent or in combination) and cisplatin – Haematologic toxicities

Nadir ANC <500 /mm^3 and nadir platelets ≥ 50,000 /mm^3	75% of previous dose (both pemetrexed and cisplatin)
Nadir platelets <50,000 /mm^3 regardless of nadir ANC	75% of previous dose (both pemetrexed and cisplatin)
Nadir platelets <50,000/mm^3 with bleeding [a], regardless of nadir ANC	50% of previous dose (both pemetrexed and cisplatin)

[a] These criteria meet the National Cancer Institute Common Toxicity Criteria (CTC v2.0; NCI 1998) definition of ≥ CTC Grade 2 bleeding

If patients develop non-haematologic toxicities ≥ Grade 3 (excluding neurotoxicity), pemetrexed 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 (as single agent or in combination) and cisplatin– Non-haematologic toxicities [a, b]

	Dose of pemetrexed (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 v2.0; NCI 1998)

[b] Excluding neurotoxicity

In the event of neurotoxicity, the recommended dose adjustment for pemetrexed 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 (as single agent or in combination) and cisplatin – Neurotoxicity

CTC [a] Grade	Dose of pemetrexed (mg/m^2)	Dose for cisplatin (mg/m^2)
0 – 1	100% of previous dose	100% of previous dose
2	100% of previous dose	50% of previous dose

[a] National Cancer Institute Common Toxicity Criteria (CTC v2.0; NCI 1998)

Treatment with pemetrexed should be discontinued if a patient experiences any haematologic or non-haematologic Grade 3 or 4 toxicity after 2 dose reductions or immediately if Grade 3 or 4 neurotoxicity is observed.

Special populations

Elderly

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

Paediatric population

There is no relevant use of pemetrexed in the paediatric population in malignant pleural mesothelioma and non-small cell lung cancer.

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 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 pemetrexed 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 aminotransferase >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 is for intravenous use. Pemetrexed should be administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Breast-feeding (see section 4.6).

Concomitant yellow fever vaccine (see section 4.5).

4.4 Special warnings and precautions for use

Pemetrexed can suppress bone marrow function as manifested by neutropenia, thrombocytopenia and anaemia (or pancytopenia) (see section 4.8). Myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for myelosuppression during therapy and pemetrexed 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).

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 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 below 45 ml/min. Therefore, the use of pemetrexed 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 non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, and acetylsalicylic acid (>1.3 g daily) for 2 days before, on the day of, and 2 days following pemetrexed administration (see section 4.5).

In patients with mild to moderate renal insufficiency eligible for pemetrexed 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 following pemetrexed administration (see section 4.5).

Serious renal events, including acute renal failure, have been reported with pemetrexed alone or in association with other chemotherapeutic agents. Many of the patients in whom these occurred had underlying risk factors for the development of renal events including dehydration or pre-existing hypertension or diabetes. Nephrogenic diabetes insipidus and renal tubular necrosis were also reported in post marketing setting with pemetrexed alone or with other chemotherapeutic agents. 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. A phase 2 study of pemetrexed in 31 solid tumour patients with stable third space fluid demonstrated no difference in pemetrexed dose normalized plasma concentrations or clearance compared to patients without third space fluid collections. Thus, drainage of third space fluid collection prior to pemetrexed treatment should be considered, but may not be necessary.

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.

Serious cardiovascular events, including myocardial infarction and cerebrovascular events have been uncommonly reported during clinical studies with pemetrexed, usually when given in combination with another cytotoxic agent. Most of the patients in whom these events have been 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 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. 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 and for 6 months following completion of treatment (see section 4.6).

Cases of radiation pneumonitis have been reported in patients treated with radiation either prior, during or subsequent to their pemetrexed therapy. Particular attention should be paid to these patients and caution exercised with use of other radiosensitising agents.

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

Excipients

Pemetrexed 100 mg powder for concentrate for solution for infusion

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium- free'.

Pemetrexed 500 mg powder for concentrate for solution for infusion

This medicinal product contains 54 mg sodium per vial, equivalent to 2.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Pemetrexed is mainly eliminated unchanged renally by tubular secretion and to a lesser extent by glomerular filtration. Concomitant administration of nephrotoxic drugs (e.g. aminoglycoside, loop diuretics, platinum compounds, cyclosporin) could

potentially result in delayed clearance of pemetrexed. This combination should be used with caution. If necessary, creatinine clearance should be closely monitored.

Concomitant administration of substances that are also tubularly secreted (e.g. probenecid, penicillin) could potentially result in delayed clearance of pemetrexed. Caution should be made when these drugs are combined with pemetrexed. 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 >1600 mg/day) and acetylsalicylic acid at higher dose (≥1.3 g daily) may decrease pemetrexed elimination and, consequently, increase the occurrence of pemetrexed adverse reactions. Therefore, caution should be made when administering higher doses of NSAIDs or acetylsalicylic acid, concurrently with pemetrexed to patients with normal function (creatinine clearance ≥80 ml/min).

In patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 ml/min), the concomitant administration of pemetrexed with NSAIDs (e.g. ibuprofen) or acetylsalicylic acid at higher dose should be avoided for 2 days before, on the day of, and 2 days following pemetrexed administration (see section 4.4).

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

Pemetrexed undergoes limited hepatic metabolism. Results from *in vitro* studies with human liver microsomes indicated that pemetrexed would not be predicted to cause clinically significant inhibition of the metabolic clearance of drugs metabolised by CYP3A, CYP2D6, CYP2C9, and CYP1A2.

Interactions common to all cytotoxics

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

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

Concomitant use not recommended: Live attenuated vaccines (except yellow fever, for which concomitant use is contraindicated): risk of systemic, possibly fatal, disease. The risk is increased in subjects who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where it exists (poliomyelitis) (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Pemetrexed can have genetically damaging effects. Woman of childbearing potential must be use effective contraception during treatment with pemetrexed and for 6 months following completion of treatment.

Sexually mature males are advised to use effective contraceptive measures and not to father a child during the treatment and up to 3 months thereafter.