**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Pemetrexed Sandoz 100 mg powder for concentrate for solution for infusion
Pemetrexed Sandoz 500 mg powder for concentrate for solution for infusion
Pemetrexed Sandoz 1000 mg powder for concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pemetrexed Sandoz 100 mg powder for concentrate for solution for infusion
One vial of powder contains 100 mg of pemetrexed (as disodium).

*Excipient with known effect*
One vial of powder contains approximately 11 mg of sodium.

Pemetrexed Sandoz 500 mg powder for concentrate for solution for infusion
One vial of powder contains 500 mg of pemetrexed (as disodium).

*Excipient with known effect*
One vial of powder contains approximately 54 mg of sodium.

Pemetrexed Sandoz 1000 mg powder for concentrate for solution for infusion
One vial of powder contains 1000 mg of pemetrexed (as disodium).

*Excipient with known effect*
One vial of powder contains approximately 108 mg of 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 off-white or pale yellow lyophilised powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

Non-small cell lung cancer
Pemetrexed Sandoz 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 Sandoz 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 Sandoz 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

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

Posology

*Pemetrexed Sandoz 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 antiemetic treatment and appropriate hydration prior to and/or after receiving cisplatin (see also cisplatin Summary of Product Characteristics for specific dosing advice).

*Pemetrexed Sandoz 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 1,000 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 $B_{12}$ (1,000 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 ≥ 1,500 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 re-treated using the guidelines in Tables 1, 2, and 3, which are applicable for Pemetrexed Sandoz used as a single agent or in combination with cisplatin.

| **Table 1. Dose modification table for Pemetrexed Sandoz (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 Sandoz 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 Sandoz (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)<br>[b] Excluding neurotoxicity | | |

In the event of neurotoxicity, the recommended dose adjustment for Pemetrexed Sandoz 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 Sandoz (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 Sandoz 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 reactions 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 Sandoz is for intravenous use. Pemetrexed Sandoz 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 Sandoz, and for instructions on reconstitution and dilution of the medicinal product 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 ≥ 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 B12 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 < 45ml/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 normalised 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 anti-emetic 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 3 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 Sandoz 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 Sandoz 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.

*Pemetrexed Sandoz 1000 mg powder for concentrate for solution for infusion*
This medicinal product contains 108 mg sodium per vial, equivalent to 5.4% 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 medicinal products (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 medicinal products 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 rections. 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 medicinal products 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 anti-cancer 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. Women of childbearing potential must 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.

Pregnancy
There are no data from the use of pemetrexed 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 toxicity (see section 5.3). Pemetrexed should not be used during pregnancy unless clearly necessary, after a careful consideration of the needs of the mother and the risk for the foetus (see section 4.4).

Breast-feeding
It is unknown whether pemetrexed is excreted in human milk, and adverse reactions on the breast-feeding child cannot be excluded. Breast-feeding must be discontinued during pemetrexed therapy (see section 4.3).

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

## 4.7 Effects on 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 may cause fatigue. Therefore, patients should be cautioned against driving or operating machines if this event occurs.

## 4.8 Undesirable effects

Summary of the safety profile
The most commonly reported undesirable effects related to pemetrexed, whether used as monotherapy or in combination, are bone marrow suppression manifested as anaemia, neutropenia, leukopenia, thrombocytopenia; and gastrointestinal toxicities, manifested as anorexia, nausea, vomiting, diarrhoea, constipation, pharyngitis, mucositis, and stomatitis. Other undesirable effects include renal toxicities, increased aminotransferases, alopecia, fatigue, dehydration, rash, infection/sepsis and neuropathy. Rarely seen events include Stevens-Johnson syndrome and toxic epidermal necrolysis.
The table 4 lists the adverse drug events regardless of causality associated with pemetrexed used either as a monotherapy treatment or in combination with cisplatin from the pivotal registration studies (JMCH, JMEI, JMBD, JMEN and PARAMOUNT) and from the post marketing period.

ADRs are listed by MedDRA body system organ class. The following convention has been used for classification of frequency:
very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from available data).

**Table 4.** Frequencies of all grades adverse drug events regardless of causality from the pivotal registration studies: JMEI (ALIMTA vs Docetaxel), JMDB (ALIMTA and Cisplatin versus GEMZAR and Cisplatin, JMCH (ALIMTA plus Cisplatin versus Cisplatin), JMEN and PARAMOUNT (Pemetrexed plus Best Supportive Care versus Placebo plus Best Supportive Care) and from post-marketing period**.**

| **System Organ Class (MedDRA)** | **Very common** | **Common** | **Uncommon** | **Rare** | **Very rare** | **Not known** |
|---|---|---|---|---|---|---|
| Infections and infestations | Infection[a]<br>Pharyngitis | Sepsis[b] | | | Dermo-hypodermitis | |
| Blood and lymphatic system disorders | Neutropenia<br>Leukopenia<br>Haemoglobin decreased | Febrile neutropenia<br>Platelet count decreased | Pancytopenia | Autoimmune haemolytic anaemia | | |
| Immune System disorders | | Hypersensiti-vity | | Anaphylac-tic shock | | |
| Metabolism and nutrition disorders | | Dehydration | | | | |
| Nervous system disorders | | Taste disorder<br>Peripheral motor neuropathy<br>Peripheral sensory neuropathy<br>Dizziness | Cerebrovascular accident<br>Ischaemic stroke<br>Haemorrhage intracranial | | | |
| Eye disorders | | Conjunctivitis<br>Dry eye<br>Lacrimation increased<br>Keratoconjunctivitis sicca<br>Eyelid oedema<br>Ocular surface disease | | | | |
| Cardiac disorders | | Cardiac failure<br>Arrhythmia | Angina<br>Myocardial infarction<br><br>Coronary artery disease<br>Arrhythmia supraventricular | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Vascular disorders | | | Peripheral ischaemia[c] | | | |
| Respiratory, thoracic and mediastinal disorders | | | Pulmonary embolism<br>Interstitial pneumonitis[bd] | | | |
| Gastrointes-tinal disorders | Stomatitis<br>Anorexia<br>Vomiting<br>Diarrhoea<br>Nausea | Dyspepsia<br>Constipation<br>Abdominal pain | Rectal haemorrhage<br>Gastrointestinal haemorrhage<br>Intestinal perforation<br>Oesophagitis<br>Colitis [e] | | | |
| Hepatobiliary disorders | | Aalanine aminotransferase increased<br>Aspartate aminotransferase increased | | Hepatitis | | |
| Skin and subcutaneous tissue disorders | Rash<br>Skin exfoliation | Hyperpigmentation<br>Pruritus<br>Erythema multiforme<br>Alopecia<br>Urticaria | | Erythema | Stevens-Johnson syndrome[b]<br>Toxic epidermal necrolysis[b]<br>Pemphigoid<br>Dermatitis bullous<br>Acquired epidermolysis bullosa<br>Erythema-tous oedema[f]<br>Pseudocellu-litis<br>Dermatitis<br>Eczema<br>Prurigo | |
| Renal and urinary disorders | Creatinine clearance decreased<br>Blood creatinine increased[e] | Renal failure<br>Glomerular filtration rate decreased | | | | Nephroge-nic diabetes insipidus<br><br>Renal tubular necrosis |
| General disorders and administration site conditions | Fatigue | Pyrexia<br>Pain<br>Oedema<br>Chest pain<br>Mucosal inflammation | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Investigations | | Gamma-glutamyltransferase increased | | | | |
| Injury, poisoning and procedural complications | | | Radiation oesophagitis Radiation pneumonitis | Recall phenomenon | | |

[a] with and without neutropenia
[b] in some cases fatal
[c] sometimes leading to extremity necrosis
[d] with respiratory insufficiency
[e]seen only in combination with cisplatin
[f] mainly of the lower limbs

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

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. In the event of suspected overdose, patients should be monitored with blood counts and should receive supportive therapy as necessary. The use of calcium folinate / folinic acid in the management of pemetrexed overdose should be considered.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Folic acid analogues, ATC code: L01BA04

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

*In vitro* studies have shown that pemetrexed behaves as a multi-targeted 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 synthetase. 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 medicinal product action in malignant cells.

The European Medicines Agency has waived the obligation to submit the results of studies with Pemetrexed in all subsets of the paediatric population in the granted indications (see Section 4.2).

Clinical efficacy

*Mesothelioma*
EMPHACIS, a multi-centre, randomised, single-blind Phase 3 study of pemetrexed plus cisplatin versus cisplatin in chemonaive patients with malignant pleural mesothelioma, has shown that patients treated with pemetrexed and cisplatin had a clinically meaningful 2.8-month median survival advantage over patients receiving cisplatin alone.

During the study, low-dose folic acid and vitamin $B_{12}$ supplementation was introduced to patients' therapy to reduce toxicity. The primary analysis of this study was performed on the population of all patients randomly assigned to a treatment arm who received study substance (randomised and treated). A subgroup analysis was performed on patients who received folic acid and vitamin $B_{12}$ supplementation during the entire course of study therapy (fully supplemented). The results of these analyses of efficacy are summarised in the table below.

**Table 5 - Efficacy of pemetrexed plus cisplatin vs. cisplatin in malignant pleural mesothelioma**

| | **Randomised and treated patients** | | **Fully supplemented patients** | |
|---|---|---|---|---|
| **Efficacy parameter** | **Pemetrexed/ Cisplatin (N = 226)** | **Cisplatin (N = 222)** | **Pemetrexed/ Cisplatin (N = 168)** | **Cisplatin (N = 163)** |
| Median overall survival (months) | 12.1 | 9.3 | 13.3 | 10.0 |
| (95% CI) | (10.0-14.4) | (7.8-10.7) | (11.4-14.9) | (8.4-11.9) |
| Log rank *p*-value* | 0.020 | | 0.051 | |
| Median time to tumour progression (months) | 5.7 | 3.9 | 6.1 | 3.9 |
| (95% CI) | (4.9-6.5) | (2.8-4.4) | (5.3-7.0) | (2.8-4.5) |
| Log rank *p*-value* | 0.001 | | 0.008 | |
| Time to treatment failure (months) | 4.5 | 2.7 | 4.7 | 2.7 |
| (95% CI) | (3.9-4.9) | (2.1-2.9) | (4.3-5.6) | (2.2-3.1) |
| Log rank *p*-value* | 0.001 | | 0.001 | |
| Overall response rate** | 41.3% | 16.7% | 45.5% | 19.6% |
| (95% CI) | (34.8-48.1) | (12.0-22.2) | (37.8-53.4) | (13.8-26.6) |
| Fisher's exact *p*-value* | < 0.001 | | < 0.001 | |

Abbreviation: CI = confidence interval.
**p*-value refers to comparison between arms.
***In the pemetrexed/cisplatin arm, randomised and treated (N=225) and fully supplemented (N=167).

A statistically significant improvement of the clinically relevant symptoms (pain and dyspnoea) associated with malignant pleural mesothelioma in the pemetrexed/cisplatin arm (212 patients) versus the cisplatin arm alone (218 patients) was demonstrated using the Lung Cancer Symptom Scale. Statistically significant differences in pulmonary function tests were also observed. The separation between the treatment arms was achieved by improvement in lung function in the pemetrexed/cisplatin arm and deterioration of lung function over time in the control arm.

There are limited data in patients with malignant pleural mesothelioma treated with pemetrexed alone. Pemetrexed at a dose of 500 mg/m$^2$ was studied as a single agent in 64 chemonaive patients with malignant pleural mesothelioma. The overall response rate was 14.1%.

*NSCLC, second-line treatment*
A multi-centre, randomised, open-label Phase 3 study of pemetrexed versus docetaxel in patients with locally advanced or metastatic NSCLC after prior chemotherapy has shown median survival times of 8.3 months for patients treated with pemetrexed (Intent-To-Treat [ITT] population N = 283) and 7.9 months for patients treated with docetaxel (ITT N = 288). Prior chemotherapy did not include pemetrexed. An analysis of the impact of NSCLC histology on the treatment effect on overall survival was in favour of pemetrexed versus docetaxel for other than predominantly squamous histologies (N = 399, 9.3 versus 8.0 months, adjusted hazard ratio (HR) = 0.78; 95% CI = 0.61-1.00, p = 0.047) and was in favour of docetaxel for squamous cell carcinoma histology (N =172, 6.2 versus 7.4 months, adjusted HR = 1.56; 95% CI = 1.08-2.26, p = 0.018). There were no clinically relevant differences observed for the safety profile of pemetrexed within the histology subgroups.

Limited clinical data from a separate randomised, Phase 3, controlled trial, suggest that efficacy data (overall survival, progression-free survival) for pemetrexed are similar between patients previously pre-treated with docetaxel (N = 41) and patients who did not receive previous docetaxel treatment (N = 540).

**Table 6: Efficacy of pemetrexed vs. docetaxel in NSCLC - ITT population**

| | **Pemetrexed** | **Docetaxel** |
|---|---|---|
| **Survival time (months)**<br>• Median (m)<br>• 95% CI for median | (N = 283)<br>8.3<br>(7.0-9.4) | (N = 288)<br>7.9<br>(6.3-9.2) |
| • HR<br>• 95% CI for HR<br>• Non-inferiority *p*-value (HR) | 0.99<br>(0.82-1.20)<br>0.226 | |
| **Progression-free survival (months)**<br>• Median | (N = 283)<br>2.9 | (N = 288)<br>2.9 |
| • HR (95% CI) | 0.97 (0.82-1.16) | |
| **Time to treatment failure (TTTF - months)**<br>• Median | (N = 283)<br>2.3 | (N = 288)<br>2.1 |
| • HR (95% CI) | 0.84 (0.71-0.997) | |
| **Response** (n: qualified for response)<br>• Response rate (%) (95% CI)<br>• Stable disease (%) | (N = 264)<br>9.1 (5.9-13.2)<br>45.8 | (N = 274)<br>8.8 (5.7-12.8)<br>46.4 |
| Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; N = total population size. | | |

*NSCLC, first-line treatment*
A multi-centre, randomised, open-label, Phase 3 study of pemetrexed plus cisplatin versus gemcitabine plus cisplatin in chemonaive patients with locally advanced or metastatic (Stage IIIb or IV) non-small cell lung cancer (NSCLC) showed that pemetrexed plus cisplatin (Intent-To-Treat [ITT] population N = 862) met its primary endpoint and showed similar clinical efficacy as gemcitabine plus cisplatin (ITT N = 863) in overall survival (adjusted hazard ratio (HR) 0.94; 95% CI= 0.84-1.05). All patients included in this study had an ECOG performance status 0 or 1.
The primary efficacy analysis was based on the ITT population. Sensitivity analyses of main efficacy endpoints were also assessed on the Protocol Qualified (PQ) population. The efficacy analyses using PQ population are consistent with the analyses for the ITT population and support the non-inferiority of AC versus GC.
Progression-free survival (PFS) and overall response rate were similar between treatment arms: median PFS was 4.8 months for pemetrexed plus cisplatin versus 5.1 months for gemcitabine plus cisplatin (adjusted hazard ratio (HR) 1.04; 95% CI= 0.94-1.15), and overall response rate was 30.6% (95% CI= 27.3- 33.9) for pemetrexed plus cisplatin versus 28.2% (95% CI= 25.0-31.4) for gemcitabine plus cisplatin. PFS data were partially confirmed by an independent review (400/1725 patients were randomly selected for review).

The analysis of the impact of NSCLC histology on overall survival demonstrated clinically relevant differences in survival according to histology, see table below.

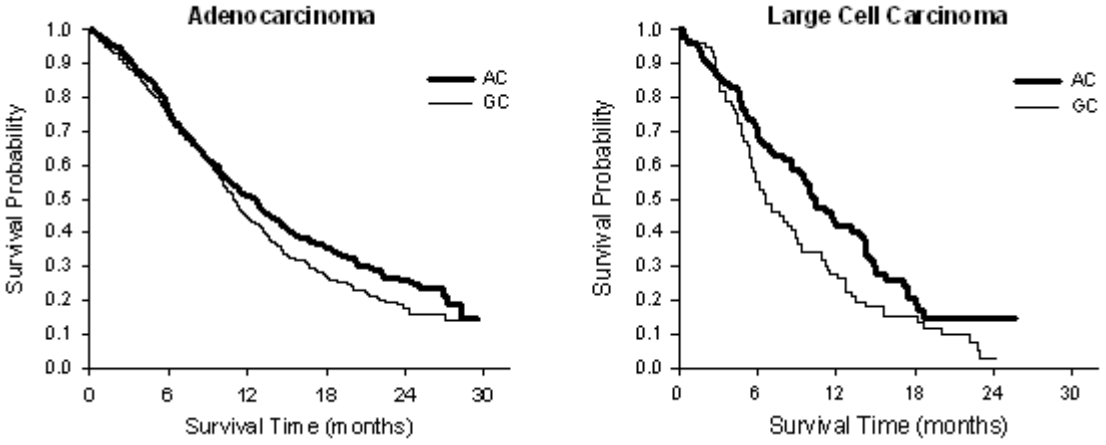
**Table 7: Efficacy of pemetrexed + cisplatin vs. gemcitabine + cisplatin in first-line non-small cell lung cancer – ITT population and histology subgroups**

| ITT population and histology subgroups | Median overall survival in months (95% CI) | | | | Adjusted hazard ratio (HR) (95% CI) | Superiority *p*-value |
|---|---|---|---|---|---|---|
| | Pemetrexed + Cisplatin | | Gemcitabine + Cisplatin | | | |
| ITT population (N = 1725) | 10.3 (9.8 – 11.2) | N = 862 | 10.3 (9.6 – 10.9) | N = 863 | 0.94[a] (0.84 – 1.05) | 0.259 |
| Adenocarcinoma (N = 847) | 12.6 (10.7 – 13.6) | N = 436 | 10.9 (10.2 –11.9) | N = 411 | 0.84 (0.71–0.99) | 0.033 |
| Large cell (N = 153) | 10.4 (8.6 – 14.1) | N = 76 | 6.7 (5.5 – 9.0) | N = 77 | 0.67 (0.48–0.96) | 0.027 |
| Other (N = 252) | 8.6 (6.8 – 10.2) | N = 106 | 9.2 (8.1 – 10.6) | N = 146 | 1.08 (0.81–1.45) | 0.586 |
| Squamous cell (N = 473) | 9.4 (8.4 – 10.2) | N = 244 | 10.8 (9.5 – 12.1) | N = 229 | 1.23 (1.00–1.51) | 0.050 |

Abbreviations: CI = confidence interval; ITT = intent-to-treat; N = total population size.

[a] Statistically significant for non-inferiority, with the entire confidence interval for HR well below the 1.17645 non-inferiority margin ($p < 0.001$).

**Kaplan-Meier plots of overall survival by histology**




There were no clinically relevant differences observed for the safety profile of pemetrexed plus cisplatin within the histology subgroups.

Patients treated with pemetrexed and cisplatin required fewer transfusions (16.4% versus 28.9%, p < 0.001), red blood cell transfusions (16.1% versus 27.3%, p < 0.001) and platelet transfusions (1.8% versus 4.5%, p = 0.002). Patients also required lower administration of erythropoietin/darbopoietin (10.4% versus 18.1%, p < 0.001), G-CSF/GM-CSF (3.1% versus 6.1%, p = 0.004), and iron preparations (4.3% versus 7.0%, p = 0.021).

*NSCLC, maintenance treatment*

JMEN

A multi-centre, randomised, double-blind, placebo-controlled Phase 3 study (JMEN), compared the efficacy and safety of maintenance treatment with pemetrexed plus best supportive care (BSC) (N = 441) with that of placebo plus BSC (N = 222) in patients with locally advanced (Stage IIIB) or metastatic (Stage IV) Non-Small Cell Lung Cancer (NSCLC) who did not progress after 4 cycles of first-line doublet therapy containing Cisplatin or Carboplatin in combination with Gemcitabine,

Paclitaxel, or Docetaxel. First-line doublet therapy containing pemetrexed was not included. All patients included in this study had an ECOG performance status 0 or 1. Patients received maintenance treatment until disease progression. Efficacy and safety were measured from the time of randomisation after completion of first-line (induction) therapy. Patients received a median of 5 cycles of maintenance treatment with pemetrexed and 3.5 cycles of placebo. A total of 213 patients (48.3%) completed ≥ 6 cycles and a total of 103 patients (23.4%) completed ≥ 10 cycles of treatment with pemetrexed.

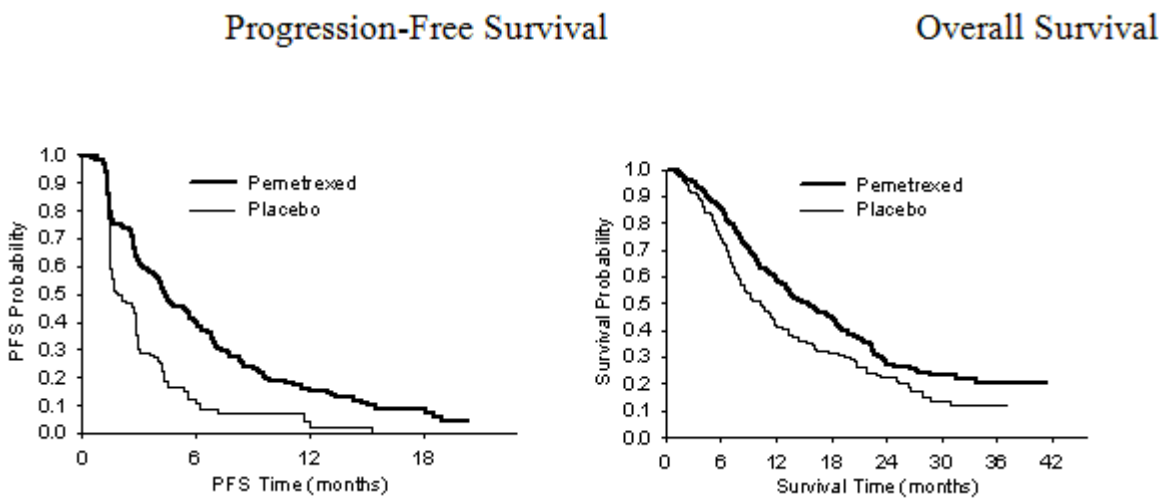
The study met its primary endpoint and showed a statistically significant improvement in PFS in the pemetrexed arm over the placebo arm (N = 581, independently reviewed population; median of 4.0 months and 2.0 months, respectively) (hazard ratio = 0.60,95% CI = 0.49-0.73, p < 0.00001). The independent review of patient scans confirmed the findings of the investigator assessment of PFS. The median OS for the overall population (N = 663) was 13.4 months for the pemetrexed arm and 10.6 months for the placebo arm, hazard ratio = 0.79 (95% CI= 0.65-0.95, p = 0.01192).

Consistent with other pemetrexed studies, a difference in efficacy according to NSCLC histology was observed in JMEN. For patients with NSCLC other than predominantly squamous cell histology (N = 430, independently reviewed population) median PFS was 4.4 months for the pemetrexed arm and 1.8 months for the placebo arm, hazard ratio = 0.47 (95% CI = 0.37-0.60, p = 0.00001). The median OS for patients with NSCLC other than predominantly squamous cell histology (N = 481) was 15.5 months for the pemetrexed arm and 10.3 months for the placebo arm, hazard ratio = 0.70 (95% CI = 0.56-0.88, p = 0.002). Including the induction phase, the median OS for patients with NSCLC other than predominantly squamous cell histology was 18.6 months for the pemetrexed arm and 13.6 months for the placebo arm, hazard ratio = 0.71 (95% CI = 0.56-0.88, p = 0.002).

The PFS and OS results in patients with squamous cell histology suggested no advantage for pemetrexed over placebo.

There were no clinically relevant differences observed for the safety profile of pemetrexed within the histology subgroups.

**JMEN: Kaplan-Meier plots of progression-free survival (PFS) and overall survival pemetrexed versus placebo in patients with NSCLC other than predominantly squamous cell histology:**




PARAMOUNT

A multi-centre, randomised, double-blind, placebo-controlled Phase 3 study (PARAMOUNT), compared the efficacy and safety of continuation maintenance treatment with pemetrexed plus BSC (N = 359) with that of placebo plus BSC (N = 180) in patients with locally advanced (Stage IIIB) or metastatic (Stage IV) NSCLC other than predominantly squamous cell histology who did not progress after 4 cycles of first-line doublet therapy of pemetrexed in combination with cisplatin. Of the 939 patients treated with pemetrexed plus cisplatin induction, 539 patients were randomised to maintenance treatment with pemetrexed or placebo. Of the randomised patients, 44.9% had a

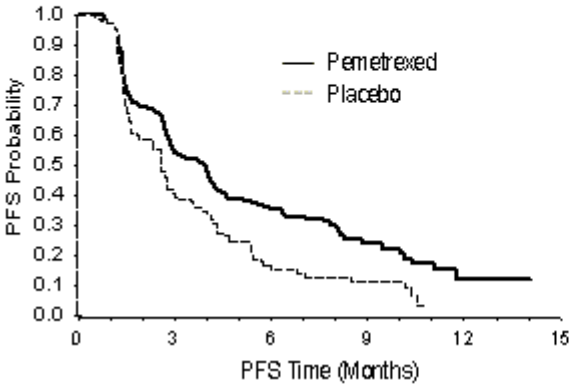
complete/partial response and 51.9% had a response of stable disease to pemetrexed plus cisplatin induction. Patients randomised to maintenance treatment were required to have an ECOG performance status 0 or 1. The median time from the start of pemetrexed plus cisplatin induction therapy to the start of maintenance treatment was 2.96 months on both the pemetrexed arm and the placebo arm. Randomised patients received maintenance treatment until disease progression. Efficacy and safety were measured from the time of randomisation after completion of first-line (induction) therapy. Patients received a median of 4 cycles of maintenance treatment with pemetrexed and 4 cycles of placebo. A total of 169 patients (47.1%) completed ≥ 6 cycles maintenance treatment with pemetrexed, representing at least 10 total cycles of pemetrexed.

The study met its primary endpoint and showed a statistically significant improvement in PFS in the pemetrexed arm over the placebo arm (N = 472, independently reviewed population; median of 3.9 months and 2.6 months, respectively) (hazard ratio = 0.64, 95% CI = 0.51-0.81, p = 0.0002). The independent review of patient scans confirmed the findings of the investigator assessment of PFS. For randomised patients, as measured from the start of pemetrexed plus cisplatin first-line induction treatment, the median investigator-assessed PFS was 6.9 months for the pemetrexed arm and 5.6 months for the placebo arm (hazard ratio = 0.59, 95% CI = 0.47-0.74).

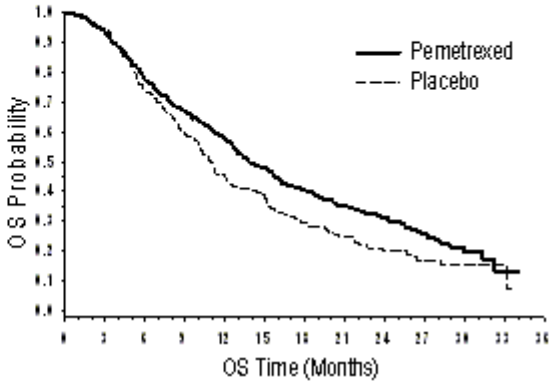
Following pemetrexed plus cisplatin induction (4 cycles), treatment with pemetrexed was statistically superior to placebo for OS (median 13.9 months versus 11.0 months, hazard ratio = 0.78, 95%CI=0.64-0.96, p=0.0195). At the time of this final survival analysis, 28.7% of patients were alive or lost to follow up on the pemetrexed arm versus 21.7% on the placebo arm. The relative treatment effect of pemetrexed was internally consistent across subgroups (including disease stage, induction response, ECOG PS, smoking status, gender, histology and age) and similar to that observed in the unadjusted OS and PFS analyses. The 1 year and 2 year survival rates for patients on pemetrexed were 58% and 32% respectively, compared to 45% and 21% for patients on placebo. From the start of pemetrexed plus cisplatin first-line induction treatment, the median OS of patients was 16.9 months for the pemetrexed arm and 14.0 months for the placebo arm (hazard ratio= 0.78, 95% CI= 0.64-0.96). The percentage of patients that received post-study treatment was 64.3% for pemetrexed and 71.7% for placebo.

**PARAMOUNT: Kaplan-Meier plot of progression-free survival (PFS) and overall survival (OS) for continuation pemetrexed maintenance versus placebo in patients with NSCLC other than predominantly squamous cell histology (measured from randomisation)**

Progression Free Survival




Overall Survival




The pemetrexed maintenance safety profiles from the two studies JMEN and PARAMOUNT were similar.

## 5.2 Pharmacokinetic properties

The pharmacokinetic properties of pemetrexed following single-agent administration have been evaluated in 426 cancer patients with a variety of solid tumours at doses ranging from 0.2 to 838 mg/m$^2$ infused over a 10-minute period. Pemetrexed has a steady-state volume of distribution of 9 l/m$^2$. *In vitro* studies indicate that 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. *In vitro* studies indicate that pemetrexed is actively secreted by OAT3 (organic anion transporter). 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 90ml/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 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

Mannitol (E421)
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)

### 6.2 Incompatibilities

Pemetrexed is physically incompatible with diluents containing calcium, including lactated Ringer's injection and Ringer's injection.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life

Unopened vial
2 years

Reconstituted and infusion solution
Chemical and physical in-use stability of reconstituted solutions of Pemetrexed Sandoz has been demonstrated for 4 days at 2°C to 8°C and for 4 days below 25°C.

Chemical and physical in-use stability of infusion solutions of Pemetrexed Sandoz has been demonstrated for 4 days at 2°C to 8°C and for 2 days 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°C to 8°C, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.

## 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

## 6.5 Nature and contents of container

Pemetrexed Sandoz 100 mg powder for concentrate for solution for infusion
Clear, colorless 10 ml type I glass vial with chlorobutyl rubber stopper and aluminium crimp cap with a flip-off cap, containing 100 mg of pemetrexed.
Pack of 1 vial with protective plastic overwrap.

Pemetrexed Sandoz 500 mg powder for concentrate for solution for infusion
Clear, colorless 50 ml type I glass vial with chlorobutyl rubber stopper and aluminium crimp cap with a flip-off cap, containing 500 mg of pemetrexed.
Pack of 1 vial with protective plastic overwrap.

Pemetrexed Sandoz 1000 mg powder for concentrate for solution for infusion
Clear, colorless 100 ml type I glass vial with chlorobutyl rubber stopper and aluminium crimp cap with a flip-off cap, containing 1000 mg of pemetrexed.
Pack of 1 vial with protective plastic overwrap.

## 6.6 Special precautions for disposal and other handling

1. Use aseptic technique during the reconstitution and further dilution of pemetrexed for intravenous infusion administration.

2. Calculate the dose and the number of Pemetrexed Sandoz vials needed. Each vial contains an excess of pemetrexed to facilitate delivery of label amount.

3. Pemetrexed Sandoz 100 mg
   Reconstitute 100-mg vials with 4.2 ml of sodium chloride 9 mg/ml (0.9%) solution for injection (without preservative), resulting in a solution containing 25 mg/ml pemetrexed.

   Pemetrexed Sandoz 500 mg
   Reconstitute 500-mg vials with 20 ml of sodium chloride 9 mg/ml (0.9%) solution for injection (without preservative), resulting in a solution containing 25 mg/ml pemetrexed.

   Pemetrexed Sandoz 1000 mg
   Reconstitute 1000-mg vials with 40 ml of sodium chloride 9 mg/ml (0.9%) solution for injection (without preservative), resulting in a solution containing 25 mg/ml pemetrexed.

Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in colour from colourless to pale yellow without adversely affecting product quality. The pH of the reconstituted solution is between 6.6 and 7.8. **Further dilution is required**.

4. The appropriate volume of reconstituted pemetrexed solution must be further diluted to 100 ml with sodium chloride 9 mg/ml (0.9%) solution for injection (without preservative) or with glucose 50 mg/ml (5%) solution for injection (without preservative) and administered as an intravenous infusion over 10 minutes.

5. Pemetrexed infusion solutions prepared as directed above are compatible with polyvinyl chloride and polyolefin lined administration sets and infusion bags.

6. Parenteral medicinal products must be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.

7. Pemetrexed solutions are for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Preparation and administration precautions
As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of pemetrexed infusion solutions. The use of gloves is recommended. If a pemetrexed solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If pemetrexed solutions contact the mucous membranes, flush thoroughly with water. Pemetrexed is not a vesicant. There is not a specific antidote for extravasation of pemetrexed. There have been 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. MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
A-6250 Kundl
Austria

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1037/001
EU/1/15/1037/002
EU/1/15/1037/003

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 September 2015
Data of latest renewal: 19 August 2020

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

**ANNEX II**

**A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Ebewe Pharma GmbH Nfg. KG
Mondseestrasse 11
A-4866 Unterach
Austria

Fareva Unterach GmbH
Mondseestraße 11
A-4866 Unterach
Austria

Lek Pharmaceuticals d.d.
Verovskova 57
SI-1526 Ljubljana
Slovenia

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

## A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Pemetrexed Sandoz 100 mg powder for concentrate for solution for infusion
pemetrexed

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 100 mg of pemetrexed (as disodium).

After reconstitution each vial contains 25 mg/ml of pemetrexed.

## 3. LIST OF EXCIPIENTS

Contains mannitol (E421), hydrochloric acid and sodium hydroxide (for pH adjustment).

See package leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion.
1 vial

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
For intravenous use after reconstitution and dilution.
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

**8. EXPIRY DATE**

EXP
Read the leaflet for the shelf life of the reconstituted product.

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
Austria

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/15/1037/001

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Pemetrexed Sandoz 100 mg powder for concentrate for solution for infusion
pemetrexed
Intravenous use after reconstitution and dilution

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP
Read the leaflet for the shelf life of the reconstituted product.

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Pemetrexed Sandoz 500 mg powder for concentrate for solution for infusion
pemetrexed

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

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

After reconstitution each vial contains 25 mg/ml of pemetrexed.

**3. LIST OF EXCIPIENTS**

Contains mannitol (E421), hydrochloric acid and sodium hydroxide (for pH adjustment).

See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder for concentrate for solution for infusion.
1 vial

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For single use only.
For intravenous use after reconstitution and dilution.
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Cytotoxic

**8. EXPIRY DATE**

EXP
Read the leaflet for the shelf life of the reconstituted product.

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
Austria

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/15/1037/002

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Pemetrexed Sandoz 500 mg powder for concentrate for solution for infusion
pemetrexed
Intravenous use after reconstitution and dilution

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 mg

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Pemetrexed Sandoz 1000 mg powder for concentrate for solution for infusion
pemetrexed

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One vial contains 1000 mg of pemetrexed (as disodium).

After reconstitution each vial contains 25 mg/ml of pemetrexed.

**3. LIST OF EXCIPIENTS**

Contains mannitol (E421), hydrochloric acid and sodium hydroxide (for pH adjustment).

See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder for concentrate for solution for infusion.
1 vial

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For single use only.
For intravenous use after reconstitution and dilution.
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Cytotoxic

**8. EXPIRY DATE**

EXP
Read the leaflet for the shelf life of the reconstituted product.

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
Austria

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/15/1037/003

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Pemetrexed Sandoz 1000 mg powder for concentrate for solution for infusion
pemetrexed
Intravenous use after reconstitution and dilution

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1000 mg

## 6. OTHER

**B. PACKAGE LEAFLET**

**Package leaflet: Information for the user**

**Pemetrexed Sandoz 100 mg powder for concentrate for solution for infusion**
**Pemetrexed Sandoz 500 mg powder for concentrate for solution for infusion**
**Pemetrexed Sandoz 1000 mg powder for concentrate for solution for infusion**

pemetrexed

**Read all of this leaflet carefully before you start receiving this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Pemetrexed Sandoz is and what it is used for

Pemetrexed Sandoz is a medicine used in the treatment of cancer.
Pemetrexed Sandoz is given in combination with cisplatin, another anti-cancer medicine, as treatment for malignant pleural mesothelioma, a form of cancer that affects the lining of the lung, to patients who have not received prior chemotherapy.

Pemetrexed Sandoz is also given in combination with cisplatin for the initial treatment of patients with advanced stage of lung cancer.

Pemetrexed Sandoz can be prescribed to you if you have lung cancer at an advanced stage if your disease has responded to treatment or it remains largely unchanged after initial chemotherapy.
Pemetrexed Sandoz is also a treatment for patients with advanced stage of lung cancer whose disease has progressed after other initial chemotherapy has been used.

## 2. What you need to know before you use Pemetrexed Sandoz

**Do not use Pemetrexed Sandoz:**
- if you are allergic (hypersensitive) to pemetrexed or any of the other ingredients of this medicine (listed in section 6).
- if you are breast-feeding; you must discontinue breast-feeding during treatment with Pemetrexed Sandoz.
- if you have recently received or are about to receive a vaccine against yellow fever.

**Warnings and precautions**
Talk to your doctor or hospital pharmacist before receiving Pemetrexed Sandoz.

If you currently have or have previously had problems with your kidneys, talk to your doctor or hospital pharmacist as you may not be able to receive Pemetrexed Sandoz.
Before each infusion you will have samples of your blood taken to evaluate if you have sufficient

kidney and liver function and to check that you have enough blood cells to receive Pemetrexed Sandoz. Your doctor may decide to change the dose or delay treating you depending on your general condition and if your blood cell counts are too low. If you are also receiving cisplatin, your doctor will make sure that you are properly hydrated and receive appropriate treatment before and after receiving cisplatin to prevent vomiting.

If you have had or are going to have radiation therapy, please tell your doctor, as there may be an early or late radiation reaction with Pemetrexed Sandoz.

If you have been recently vaccinated, please tell your doctor, as this can possibly cause bad effects with Pemetrexed Sandoz.

If you have heart disease or a history of heart disease, please tell your doctor.

If you have an accumulation of fluid around your lungs, your doctor may decide to remove the fluid before giving you Pemetrexed Sandoz.

**Children and adolescents**
This medicine should not be used in children or adolescents, since there is no experience with this medicine in children and adolescents under 18 years of age.

**Other medicines and Pemetrexed Sandoz**
Please tell your doctor if you are taking any medicine for pain or inflammation (swelling), such as medicines called "nonsteroidal anti-inflammatory drugs" (NSAIDs), including medicines purchased without a doctor's prescription (such as ibuprofen). There are many sorts of NSAIDs with different durations of activity. Based on the planned date of your infusion of Pemetrexed Sandoz and/or on the status of your kidney function, your doctor needs to advise you on which medicines you can take and when you can take them. If you are unsure, ask your doctor or pharmacist if any of your medicines are NSAIDs.

Please tell your doctor or hospital pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Pregnancy**
If you are pregnant, think you may be pregnant or are planning to have a baby, **tell your doctor**. The use of Pemetrexed Sandoz should be avoided during pregnancy. Your doctor will discuss with you the potential risk of taking Pemetrexed Sandoz during pregnancy.
Women must use effective contraception during treatment with Pemetrexed Sandoz and for 6 months after receiving the last dose.

**Breast-feeding**
If you are breast-feeding, tell your doctor.
Breast-feeding must be discontinued during Pemetrexed Sandoz treatment.

**Fertility**
Men are advised not to father a child during and up to 3 months following treatment with Pemetrexed Sandoz and should therefore use effective contraception during treatment with Pemetrexed Sandoz and for up to 3 months afterwards. If you would like to father a child during the treatment or in the 3 months following receipt of treatment, seek advice from your doctor or pharmacist. Pemetrexed Sandoz can affect your ability to have children. Talk to your doctor to seek advice about sperm storage before starting your therapy.

**Driving and using machines**
Pemetrexed Sandoz may make you feel tired. Be careful when driving a car or using machines.

**Pemetrexed Sandoz contains sodium**
*Pemetrexed Sandoz 100 mg powder for concentrate for solution for infusion*

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

*Pemetrexed Sandoz 500 mg powder for concentrate for solution for infusion*
This medicine contains 54 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 2.7% of the recommended maximum daily dietary intake of sodium for an adult.

*Pemetrexed Sandoz 1000 mg powder for concentrate for solution for infusion*
This medicine contains 108 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 5.4% of the recommended maximum daily dietary intake of sodium for an adult.

## 3. How to use Pemetrexed Sandoz

The dose of Pemetrexed Sandoz is 500 mg for every square metre of your body's surface area. Your height and weight are measured to work out the surface area of your body. Your doctor will use this body surface area to work out the right dose for you. This dose may be adjusted, or treatment may be delayed depending on your blood cell counts and on your general condition. A hospital pharmacist, nurse or doctor will have mixed the Pemetrexed Sandoz powder with 9 mg/ml (0.9 %) sodium chloride solution for injection before it is given to you.

You will always receive Pemetrexed Sandoz by infusion into one of your veins. The infusion will last approximately 10 minutes.

When using Pemetrexed Sandoz in combination with cisplatin
The doctor or hospital pharmacist will work out the dose you need based on your height and weight. Cisplatin is also given by infusion into one of your veins, and is given approximately 30 minutes after the infusion of Pemetrexed Sandoz has finished. The infusion of cisplatin will last approximately 2 hours.

You should usually receive your infusion once every 3 weeks.

Additional medicines
Corticosteriods: your doctor will prescribe you steroid tablets (equivalent to 4 milligram of dexamethasone twice a day) that you will need to take on the day before, on the day of, and the day after Pemetrexed Sandoz treatment. This medicine is given to you to reduce the frequency and severity of skin reactions that you may experience during your anticancer treatment.

Vitamin supplementation: your doctor will prescribe you oral folic acid (vitamin) or a multivitamin containing folic acid (350 to 1000 micrograms) that you must take once a day while you are taking Pemetrexed Sandoz. You must take at least 5 doses during the seven days before the first dose of Pemetrexed Sandoz. You must continue taking the folic acid for 21 days after the last dose of Pemetrexed Sandoz. You will also receive an injection of vitamin B12 (1000 micrograms) in the week before administration of Pemetrexed Sandoz and then approximately every 9 weeks (corresponding to 3 courses of Pemetrexed Sandoz treatment). Vitamin B12 and folic acid are given to you to reduce the possible toxic effects of the anticancer treatment.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**You must contact your doctor immediately if you notice any of the following:**

- Fever or infection (common): if you have a temperature of 38ºC or greater, sweating or other signs of infection(since you might have less white blood cells than normal which is very common). Infection (sepsis) may be severe and could lead to death.
- If you start feeling chest pain (common) or having a fast heart rate (uncommon).
- If you have pain, redness, swelling or sores in your mouth (very common).
- Allergic reaction: if you develop skin rash (very common) / burning or prickling sensation (common), or fever (common). Rarely, skin reactions may be severe and could lead to death. Contact your doctor if you get a severe rash, or itching, or blistering (Stevens-Johnson Syndrome or Toxic epidermal necrolysis).
- If you experience tiredness, feeling faint, becoming easily breathless or if you look pale (since you might have less haemoglobin than normal which is very common).
- If you experience bleeding from the gums, nose or mouth or any bleeding that would not stop, reddish or pinkish urine, unexpected bruising (since you might have less platelets than normal which is very common).
- If you experience sudden breathlessness, intense chest pain or cough with bloody sputum (uncommon)(may indicate a blood clot in the blood vessels of the lungs)

Side effects with Pemetrexed Sandoz may include:

***Very common*** *(may affect more than 1 in 10 people)*
- Infection
- Pharyngitis (a sore throat)
- Low number of neutrophil granulocytes (a type of white blood cell)
- Low white blood cells
- Low haemoglobin level
- Diarrhoea
- Vomiting
- Pain, redness, swelling or sores in your mouth
- Nausea
- Loss of appetite
- Fatigue (tiredness)
- Skin rash
- Flaking skin
- Abnormal blood tests showing reduced functionality of kidneys

***Common*** *(may affect up to 1 in 10 people)*
- Blood infection
- Fever with low number of neutrophil granulocytes (a type of white blood cell)
- Low platelet count
- Allergic reaction
- Loss of body fluids
- Taste change
- Damage to the motor nerves which may cause muscle weakness and atrophy (wasting) primary in the arms and legs)
- Damage to the sensory nerves that may cause lost of sensation, burning pain and unsteady gait
- Dizziness
- Inflammation or swelling of the conjunctiva (the membrane that lines the eyelids and covers the white of the eye
- Dry eye
- Watery eyes
- Dryness of the conjunctiva (the membrane that lines the eyelids and covers the white of the eye) and cornea (the clear layer in front of the iris and pupil.
- Swelling of the eyelids
- Eye disorder with dryness, tearing, irritation, and/or pain
- Cardiac Failure (Condition that affects the pumping power of your heart muscles)

- Irregular heart rhythm
- Indigestion
- Constipation
- Abdominal pain
- Liver: increases in the chemicals in the blood made by the liver
- Increased skin pigmentation
- Itchy skin
- Rash on the body where each mark resembles a bullseye
- Hair loss
- Hives
- Kidney stop working
- Reduced functionality of kidney
- Fever
- Pain
- Excess fluid in body tissue, causing swelling
- Chest pain
- Inflammation and ulceration of the mucous membranes lining the digestive tract

***Uncommon*** *(may affect up to 1 in 100 people)*
- Reduction in the number of red,white blood cells and platelets
- Stroke
- Type of stroke when an artery to the brain is blocked
- Bleeding inside the skull
- Angina (Chest pain caused by reduced blood flow to the heart)
- Heart attack
- Narrowing or blockage of the coronary arteries
- Abnormal heart rythm
- Deficient blood distribution to the limbs
- Blockage in one of the pulmonary arteries in your lungs
- Inflammation and scarring of the lining of the lungs with breathing problems
- Passage of bright red blood from the anus
- Bleeding in the gastrointestinal tract
- Ruptured bowel
- Inflammation of the lining of the oesophagus
- Inflammation of the lining of the large bowel, which may be accompanied by intestinal or rectal bleeding (seen only in combination with cisplatin)
- Inflammation, edema, erythema, and erosion of the mucosal surface of the esophagus caused by radiation therapy
- Inflammation of the lung caused by radiation therapy

***Rare*** *(may affect up to 1 in 1,000 people)*
- Destruction of red blood cells
- Anaphylactic shock (severe allergic reaction)
- Inflammatory condition of the liver
- Redness of the skin
- Skin rash that develops throughout a previously irradiated area

***Very rare*** *(affect up to 1 of 10 000 people)*
- Infections of skin and soft tissues
- Stevens-Johnson syndrome (a type of severe skin and mucous membranes reaction that may be life threatening)
- Toxic epidermal necrolysis (a type of severe skin reaction that may be life threatening)
- Autoimmune disorder that results in skin rashes and blistering on the legs, arms, and abdomen
- Inflammation of the skin characterized by the presence of bullae which are filled with fluid

- Skin fragility, blisters and erosions and skin scarring
- Redness, pain and swelling mainly of the lower limbs
- Inflammation of the skin and fat beneath the skin (pseudocellulitis)
- Inflammation of the skin (dermatitis)
- Skin to become inflamed, itchy, red, cracked, and rough
- Intensely itchy spots

***Not known (****frequency cannot be estimated from the available data)*
- Form of diabetes primarily due to pathology of the kidney
- Disorder of the kidneys involving the death of tubular epithelial cells that form the renal tubules

You might have any of these symptoms and/or conditions. You must tell your doctor as soon as possible when you start experiencing any of these side effects.

If you are concerned about any side effects, talk to your doctor.

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Pemetrexed Sandoz

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP.

This medicine does not require any special storage conditions.

After reconstitution and infusion:
Chemical and physical in-use stability of reconstituted solutions of Pemetrexed Sandoz has been demonstrated for 4 days at 2°C to 8°C and for 4 days below 25°C.

Chemical and physical in-use stability of infusion solutions of Pemetrexed Sandoz has been demonstrated for 4 days at 2°C to 8°C and for 2 days 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°C to 8°C, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.

Do not use this medicine if you notice particles or a discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measurements will help protect the environment.

## 6. Contents of the pack and other information

**What Pemetrexed Sandoz contains**

The active substance is pemetrexed.

Pemetrexed Sandoz 100 mg: Each vial contains 100 milligrams of pemetrexed (as disodium).
Pemetrexed Sandoz 500 mg: Each vial contains 500 milligrams of pemetrexed (as disodium).

Pemetrexed Sandoz 1000 mg: Each vial contains 1000 milligrams of pemetrexed (as disodium).

After reconstitution, the solution contains 25 mg/ml of pemetrexed.

The other ingredients are mannitol (E421), hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment) (see section 2 “Pemetrexed Sandoz contains sodium”).

**What Pemetrexed Sandoz looks like and contents of the pack**

Pemetrexed Sandoz is a powder for concentrate for solution for infusion in a glass vial. It is a white to pale yellow lyophilised powder.

Each pack of Pemetrexed Sandoz consists of one vial with protective plastic overwrap, containing 100 mg, 500 mg or 1000 mg of pemetrexed.

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**This leaflet was last revised in**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

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The following information is intended for healthcare professionals only:

**Special precautions for disposal and other handling**

1. Use aseptic technique during the reconstitution and further dilution of pemetrexed for intravenous infusion administration.

2. Calculate the dose and the number of Pemetrexed Sandoz vials needed. Each vial contains an excess of pemetrexed to facilitate delivery of label amount.

3. Pemetrexed Sandoz 100 mg:
Reconstitute 100-mg vials with 4.2 ml of sodium chloride 9 mg/ml (0.9%) solution for injection (without preservative), resulting in a solution containing 25 mg/ml pemetrexed.

Pemetrexed Sandoz 500 mg:
Reconstitute 500-mg vials with 20 ml of sodium chloride 9 mg/ml (0.9%) solution for injection (without preservative), resulting in a solution containing 25 mg/ml pemetrexed.

Pemetrexed Sandoz 1000 mg:
Reconstitute 1000-mg vials with 40 ml of sodium chloride 9 mg/ml (0.9%) solution for injection (without preservative), resulting in a solution containing 25 mg/ml pemetrexed.

Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in colour from colourless to pale yellow without adversely affecting product quality. The pH of the reconstituted solution is between 6.6 and 7.8. **Further dilution is required**.

4. The appropriate volume of reconstituted pemetrexed solution must be further diluted to 100 ml with sodium chloride 9 mg/ml (0.9%) solution for injection (without preservative) or with glucose 50 mg/ml (5%) solution for injection (without preservative) and administered as an intravenous infusion over 10 minutes.

5. Pemetrexed infusion solutions prepared as directed above are compatible with polyvinyl chloride and polyolefin lined administration sets and infusion bags. Pemetrexed is incompatible with diluents containing calcium, including lactated Ringer's Injection and Ringer's Injection.

6. Parenteral medicinal products must be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.

7. Pemetrexed solutions are for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Preparation and administration precautions
As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of pemetrexed infusion solutions. The use of gloves is recommended. If a pemetrexed solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If pemetrexed solutions contact the mucous membranes, flush thoroughly with water. Pemetrexed is not a vesicant. There is not a specific antidote for extravasation of pemetrexed. There have been 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.