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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pemetrexed medac 100 mg powder for concentrate for solution for infusion
Pemetrexed medac 500 mg powder for concentrate for solution for infusion
Pemetrexed medac 1,000 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pemetrexed medac 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 100 mg vial contains approximately 11 mg sodium.

Pemetrexed medac 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 500 mg vial contains approximately 54 mg sodium.

Pemetrexed medac 1,000 mg powder for concentrate for solution for infusion

Each vial contains 1,000 mg of pemetrexed (as pemetrexed disodium hemipentahydrate).

Excipient with known effect
Each 1,000 mg vial contains approximately 108 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 powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Malignant pleural mesothelioma

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

Non-small cell lung cancer

Pemetrexed medac 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).

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

Posology

Pemetrexed in combination with cisplatin
The recommended dose of Pemetrexed medac is 500 mg/m² 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/m² 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 medac is 500 mg/m² BSA administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

Premedication regimen
To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed 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 – 1,000 µg) 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 µg) 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/mm³ and platelets should be ≥ 100,000 cells/mm³.

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.

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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 medac 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/mm³ and nadir platelets ≥ 50,000/mm³	75 % of previous dose (both pemetrexed and cisplatin)
Nadir platelets < 50,000/mm³ regardless of nadir ANC	75 % of previous dose (both pemetrexed and cisplatin)
Nadir platelets < 50,000/mm³ 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/m²)	**Dose for cisplatin (mg/m²)**
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 premetrexed (as single agent or in combination) and cisplatin – Neurotoxicity		
CTC[a] Grade	**Dose of premetrexed (mg/m²)**	**Dose for cisplatin (mg/ m²)**
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 reactions compared to patients younger than 65 years old. No dose reductions other than those recommended for all patients are necessary.

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Paediatric population
There is no relevant use of Pemetrexed medac 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 medac is for intravenous use. Pemetrexed medac 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 medac and for instructions on reconstitution and dilution of Pemetrexed medac 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/mm³ and platelet count returns to ≥ 100,000 cells/mm³. 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

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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 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.

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Excipients

Pemetrexed medac 100 mg powder for concentrate for solution for infusion

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 mg vial, that is to say essentially 'sodium-free'.

Pemetrexed medac 500 mg powder for concentrate for solution for infusion

This medicinal product contains 54 mg sodium per 500 mg vial, equivalent to 2.70% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Pemetrexed medac 1,000 mg powder for concentrate for solution for infusion

This medicinal product contains 108 mg sodium per 1,000 mg vial, equivalent to 5.40% 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 pemetrexed with OAT3 (organic anion transporter 3) inhibitors (e.g. probenecid, penicillin, proton pump inhibitors (PPIs)) results in delayed clearance of pemetrexed. Caution should be made when these drugs are combined with pemetrexed.

In patients with normal renal function (creatinine clearance ≥ 80 ml/min), high doses of non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen > 1,600 mg/day) and acetylsalicylic acid at higher dose (≥ 1.3 g daily) may decrease pemetrexed elimination and, consequently, increase the occurrence of pemetrexed adverse 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

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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 vaccine 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.

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Tabulated list of adverse reactions

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 the 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] Pharyngitis	Sepsis[b]			Dermo-hypodermitis	
Blood and lymphatic system disorders	Neutropenia Leukopenia Haemoglobin decreased	Febrile neutropenia Platelet count decreased	Pancytopenia	Autoimmune haemolytic anaemia		
Immune System disorders		Hypersensiti-vity		Anaphylactic shock		
Metabolism and nutrition disorders		Dehydration				
Nervous system disorders		Taste disorder Peripheral motor neuropathy Peripheral sensory neuropathy Dizziness	Cerebrovascular accident Ischaemic stroke Haemorrhage intracranial			
Eye disorders		Conjunctivitis Dry eye Lacrimation increased Keratoconjunctivitis sicca Eyelid oedema Ocular surface disease				
Cardiac		Cardiac failure	Angina			

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disorders		Arrhythmia	Myocardial infarction Coronary artery disease Arrhythmia supraventricular			
Vascular disorders			Peripheral ischaemia[c]			
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism Interstitial pneumonitis[bd]			
Gastrointes-tinal disorders	Stomatitis Anorexia Vomiting Diarrhoea Nausea	Dyspepsia Constipation Abdominal pain	Rectal haemorrhage Gastrointestinal haemorrhage Intestinal perforation Oesophagitis Colitis [e]			
Hepatobiliary disorders		Alanine aminotransferase increased Aspartate aminotransferase increased		Hepatitis		
Skin and subcutaneous tissue disorders	Rash Skin exfoliation	Hyperpigmentation Pruritus Erythema multiforme Alopecia Urticaria		Erythema	Stevens-Johnson syndrome[b] Toxic epidermal necrolysis[b] Pemphigoid Dermatitis bullous Acquired epidermolysis bullosa Erythema-tous oedema[f] Pseudocellulitis Dermatitis Eczema Prurigo	
Renal and urinary disorders	Creatinine clearance decreased Blood creatinine increased[e]	Renal failure Glomerular filtration rate decreased				Nephroge-nic diabetes insipidus Renal tubular necrosis

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General disorders and administration site conditions	Fatigue	Pyrexia Pain Oedema Chest pain 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: antineoplastic agents, folic acid analogues, ATC code: L01BA04

Pemetrexed medac 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 multitargeted 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 drug action in malignant cells.

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Clinical efficacy

Mesothelioma
EMPHACIS, a multicentre, 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 drug (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

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

Abbreviation: CI = confidence interval; OS = overall survival
* p-value refers to comparison between arms
** In the pemetrexed/cisplatin arm, randomized 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/m² was studied as a single-agent in 64 chemonaive patients with malignant pleural mesothelioma. The overall response rate was 14.1 %.

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Non small cell lung cancer, second-line treatment
A multicentre, randomised, open label phase 3 study of pemetrexed versus docetaxel in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy has shown median survival times of 8.3 months for patients treated with pemetrexed (Intent To Treat population n = 283) and 7.9 months for patients treated with docetaxel (Intent-To-Treat [ITT] n = 288). Prior chemotherapy did not include pemetrexed. An analysis of the impact of NSCLC histology on the treatment effect on overall survival (OS) 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 % confidence interval [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 randomized, Phase 3, controlled trial, suggest that efficacy data (OS, progression free survival [PFS]) 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)	(n = 283)	(n = 288)
• Median (m)	8.3	7.9
• 95 % CI for median	(7.0 – 9.4)	(6.3 – 9.2)
• HR	0.99	
• 95 % CI for HR	(0.82 – 1.20)	
• Non-inferiority p-value (HR)	0.226	
PFS (months)	(n = 283)	(n = 288)
• Median	2.9	2.9
• HR (95 % CI)	0.97 (0.82 – 1.16)	
Time to treatment failure (TTTF - months)	(n = 283)	(n = 288)
• Median	2.3	2.1
• HR (95 % CI)	0.84 (0.71 – 0.997)	
Response (n: qualified for response)	(n = 264)	(n = 274)
• Response rate (%)(95 % CI)	9.1 (5.9 – 13.2)	8.8 (5.7 – 12.8)
• Stable disease (%)	45.8	46.4

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent to treat; n = total population size, PFS = progression free survival

NSCLC, first-line treatment
A multicentre, 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) NSCLC showed that pemetrexed plus cisplatin (ITT population n = 862) met its primary endpoint and showed similar clinical efficacy as gemcitabine plus cisplatin (ITT n = 863) in OS (adjusted hazard ratio 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 PG versus GC.

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 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 (400/1,725 patients were randomly selected for review).

Medicinal product no longer authorised

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

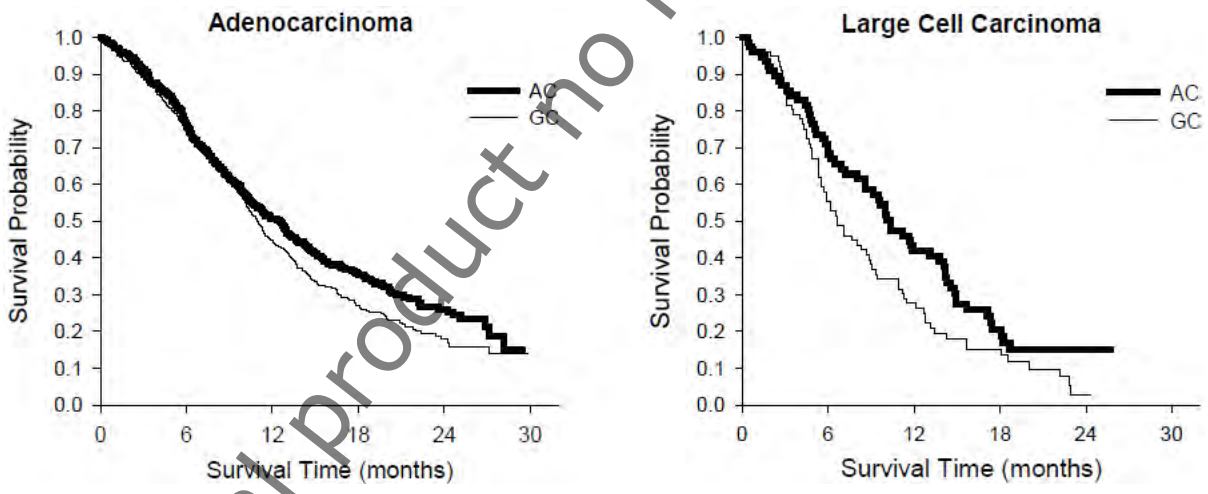
Table 7 - Efficacy of pemetrexed + cisplatin vs. gemcitabine + cisplatin in first-line non-small cell lung cancer – ITT population and histology subgroups

ITT population and histology subgroups	Median OS in months (95 % CI)				Adjusted HR (95 % CI)	Superiority p-value
	Pemetrexed + cisplatin		Gemcitabine + cisplatin			
ITT population (N = 1,725)	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; HR = hazard ratio; ITT = intent-to-treat; N = total population size; OS = overall survival

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

Kaplan Meier plots of OS 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 multicentre, 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) 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

Medicinal product no longer authorised

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.

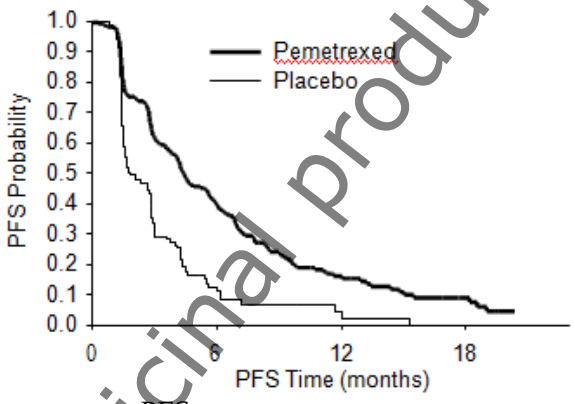
The study met its primary endpoint and showed a statistically significant improvement in PFS in the pemetrexed arm over the placebo arm (n = 581, independently reviewed population; median of 4.0 months and 2.0 months, respectively) (hazard ratio = 0.60, 95 % CI = 0.49 - 0.73, p < 0.00001). The independent 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).

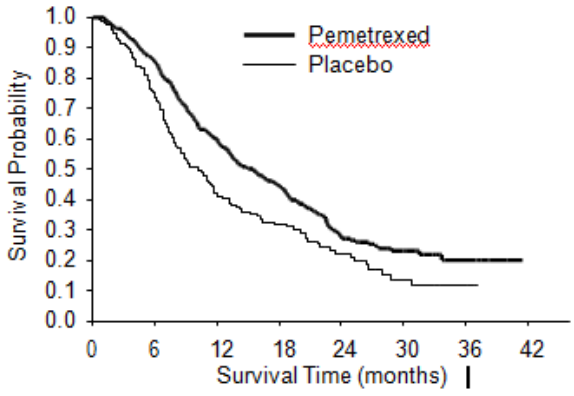
The PFS and OS results in patients with squamous cell histology suggested no advantage for pemetrexed over placebo.

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

JMEN: Kaplan Meier plots of PFS and OS pemetrexed versus placebo in patients with NSCLC other than predominantly squamous cell histology



PFS



OS

PARAMOUNT

A multicentre, 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

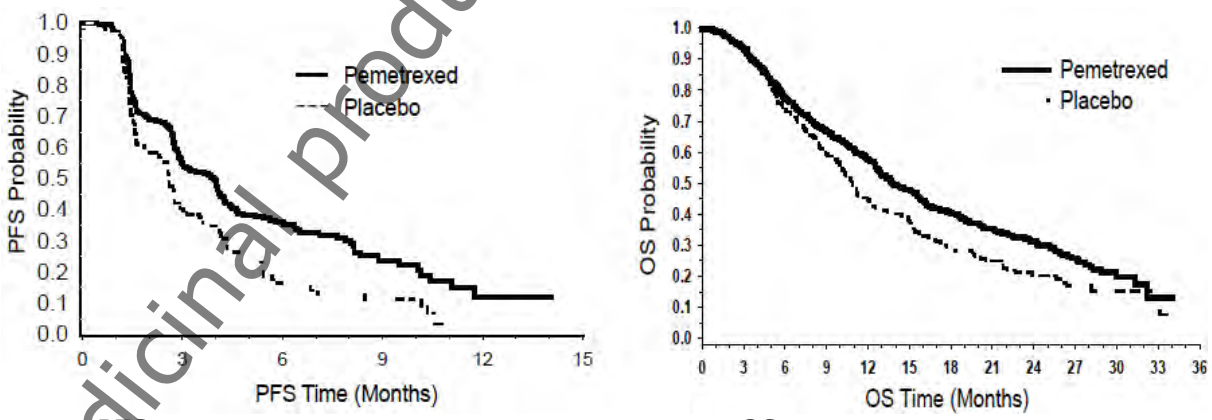
Medicinal product no longer authorised

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 PFS and OS for continuation pemetrexed maintenance versus placebo in patients with NSCLC other than predominantly squamous cell histology (measured from randomisation)



PFS OS

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

Paediatric population

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).

Medicinal product no longer authorised

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/m² infused over a 10-minute period. Pemetrexed has a steady-state volume of distribution of 9 l/m². *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 90 ml/min). Between patient variability in clearance is moderate at 19.3 %. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration increase proportionally with dose. The pharmacokinetics of pemetrexed are consistent over multiple treatment cycles.

The pharmacokinetic properties of pemetrexed are not influenced by concurrently administered cisplatin. Oral folic acid and intramuscular vitamin B_{12} supplementation do not affect the pharmacokinetics of pemetrexed.

5.3 Preclinical safety data

Administration of pemetrexed 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. In the absence of other compatibility studies this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

3 years

Medicinal product no longer authorised

Reconstituted and infusion solution

When prepared as directed, reconstituted and infusion solutions of pemetrexed contain no antimicrobial preservatives.
Chemical and physical in-use stability of reconstituted and infusion solutions of pemetrexed were demonstrated for 24 hours at refrigerated temperature.
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 not be longer than 24 hours at 2 °C to 8 °C.

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

Type I glass vial with rubber (bromobutyl rubber coated with fluoropolymer) stopper containing 100, 500 or 1,000 mg of pemetrexed.

Pack of 1 vial.

6.6 Special precautions for disposal and other handling

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

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

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

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

   Reconstitute 1,000 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 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, 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.

Medicinal product no longer authorised

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 must 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

medac Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany
Tel.: +49 4103 8006-0
Fax: +49 4103 8006-100

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1038/001 Pemetrexed medac 100 mg
EU/1/15/1038/002 Pemetrexed medac 500 mg
EU/1/15/1038/003 Pemetrexed medac 1,000 mg

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 November 2015
Date 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 https://www.ema.europa.eu.

Medicinal product no longer authorised

Medicinal product no longer authorised

ANNEX II

A. MANUFACTURER(S) 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. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release
Synthon Hispania, S.L.
C/ Castello, nº1, Pol. Las Salinas,
Sant Boi de Llobregat
08830 Barcelona, Spain

Synthon, s.r.o.
Brněnská 32/čp. 597
Blansko
678 17
Czech Republic

medac Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

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**

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 marketing authorisation holder 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.

Medicinal product no longer authorised

ANNEX III

LABELLING AND PACKAGE LEAFLET

Medicinal product no longer authorised

A. LABELLING

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

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

3. LIST OF EXCIPIENTS

Mannitol, hydrochloric acid, sodium hydroxide (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

Medicinal product no longer authorised

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

medac GmbH
Theaterstr. 6
22880 Wedel
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1038/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

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

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

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

3. LIST OF EXCIPIENTS

Mannitol, hydrochloric acid, sodium hydroxide (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

Medicinal product no longer authorised

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

medac GmbH
Theaterstr. 6
22880 Wedel
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1038/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

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

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

Pemetrexed medac 1,000 mg powder for concentrate for solution for infusion
pemetrexed

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 1,000 mg of pemetrexed (as pemetrexed disodium hemipentahydrate).

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

3. LIST OF EXCIPIENTS

Mannitol, hydrochloric acid, sodium hydroxide (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

Medicinal product no longer authorised

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

medac GmbH
Theaterstr. 6
22880 Wedel
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1038/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

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

Medicinal product no longer authorised

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial

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

Pemetrexed medac 100 mg powder for concentrate for solution for infusion
pemetrexed
Intravenous use

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

Cytotoxic.

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Vial

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

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

3. LIST OF EXCIPIENTS

Mannitol, hydrochloric acid, sodium hydroxide (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

Medicinal product no longer authorised

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

medac GmbH
Theaterstr. 6
22880 Wedel
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1038/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Vial

1. NAME OF THE MEDICINAL PRODUCT

Pemetrexed medac 1,000 mg powder for concentrate for solution for infusion
pemetrexed

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 1,000 mg of pemetrexed (as pemetrexed disodium hemipentahydrate).

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

3. LIST OF EXCIPIENTS

Mannitol, hydrochloric acid, sodium hydroxide (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

Medicinal product no longer authorised

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

medac GmbH
Theaterstr. 6
22880 Wedel
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1038/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

Medicinal product no longer authorised

B. PACKAGE LEAFLET

Medicinal product no longer authorised

Package leaflet: Information for the user

Pemetrexed medac 100 mg powder for concentrate for solution for infusion
Pemetrexed medac 500 mg powder for concentrate for solution for infusion
Pemetrexed medac 1,000 mg powder for concentrate for solution for infusion
pemetrexed

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have further questions, 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 medac is and what it is used for
2. What you need to know before you use Pemetrexed medac
3. How to use Pemetrexed medac
4. Possible side effects
5. How to store Pemetrexed medac
6. Contents of the pack and other information

1. What Pemetrexed medac is and what is it used for

Pemetrexed medac is a medicine used in the treatment of cancer.

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

Pemetrexed 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 medac 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 medac

Do not use Pemetrexed medac
- if you are allergic 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 medac.
- if you have recently received or are about to receive a vaccine against yellow fever.

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Warnings and precautions
Talk to your doctor or pharmacist before using Pemetrexed medac if:
- you currently have or have previously had problems with your kidneys, as you may not be able to receive Pemetrexed medac. 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 medac. 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.
- you have had or are going to have radiation therapy, as there may be an early or late radiation reaction with Pemetrexed medac.
- you have been recently vaccinated, as this can possibly cause bad effects with Pemetrexed medac.
- you have heart disease or a history of heart disease.
- you have an accumulation of fluid around your lungs, as your doctor may decide to remove the fluid before giving you Pemetrexed medac.

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 medac
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 medac 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 inform your doctor if you are taking medicines called proton pump inhibitors (omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole) used to treat heartburn and acid regurgitation.

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 or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. The use of Pemetrexed medac should be avoided during pregnancy. Your doctor will discuss with you the potential risk of taking Pemetrexed medac during pregnancy. Women must use effective contraception during treatment with Pemetrexed medac and for 6 months after receiving the last dose.

Breast-feeding
You should not breast-feed while using Pemetrexed medac. Discuss with your doctor when it is safe to restart breast-feeding after finishing your treatment.

Fertility
Men are advised not to father a child during and up to 3 months following treatment with Pemetrexed medac and should therefore use effective contraception during treatment with Pemetrexed medac 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 medac can affect your ability to have children. Talk to your doctor to seek advice about sperm storage before starting your therapy.

Medicinal product no longer authorised

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

Pemetrexed medac contains sodium

Pemetrexed medac 100 mg
This medicine contains less than 1 mmol sodium (23 mg) per 100 mg vial, that is to say essentially 'sodium-free'.

Pemetrexed medac 500 mg
This medicine contains 54 mg sodium (main component of cooking/table salt) in each 500 mg vial. This is equivalent to 2.70% of the recommended maximum daily dietary intake of sodium for an adult.

Pemetrexed medac 1,000 mg
This medicine contains 108 mg sodium (main component of cooking/table salt) in each 1,000 mg vial. This is equivalent to 5.40% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Pemetrexed medac

The recommend dose of Pemetrexed medac 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 medac powder with 9 mg/ml (0.9 %) sodium chloride solution for injection before it is given to you.

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

When using Pemetrexed medac 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 medac has finished. The infusion of cisplatin will last approximately 2 hours.

You should usually receive your infusion once every 3 weeks.

Additional medicines
Corticosteroids
Your doctor will prescribe you steroid tablets (equivalent to 4 mg of dexamethasone twice a day) that you will need to take on the day before, on the day of, and the day after Pemetrexed medac 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 – 1,000 µg) that you must take once a day while you are taking Pemetrexed medac. You must take at least 5 doses during the seven days before the first dose of Pemetrexed medac. You must continue taking the folic acid for 21 days after the last dose of Pemetrexed medac. You will also receive an injection of Vitamin B_{12} (1,000 µg) in the week before administration of Pemetrexed medac and then approximately every 9 weeks (corresponding to 3 courses of Pemetrexed medac treatment). Vitamin B_{12} 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.

Medicinal product no longer authorised

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 (respectively, common or very common): if you have a temperature of 38 °C 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 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)

The following side effects can occur during treatment with pemetrexed:

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
Pain, redness, swelling or sores in your mouth
Loss of appetite
Vomiting
Diarrhoea
Nausea
Skin rash
Flaking skin
Abnormal blood tests showing reduced functionality of kidneys
Fatigue (tiredness)

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

Medicinal product no longer authorised

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
Increased heart rhythm
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)

Medicinal product no longer authorised

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

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 medac

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 label and carton after EXP.

This medicine does not require any special storage conditions.

Reconstituted and infusion solutions: The product should be used immediately. When prepared as directed**,** chemical and physical in-use stability of reconstituted and infusion solutions of pemetrexed were demonstrated for 24 hours at refrigerated temperature (2 °C – 8 °C).

This medicine is for single use only; any unused solution must be disposed of in accordance with local requirement.

6. Contents of the pack and other information

What Pemetrexed medac contains

The active substance is pemetrexed.

Pemetrexed medac 100 mg: Each vial contains 100 mg of pemetrexed (as pemetrexed disodium hemipentahydrate).
Pemetrexed medac 500 mg: Each vial contains 500 mg of pemetrexed (as pemetrexed disodium hemipentahydrate).
Pemetrexed medac 1,000 mg: Each vial contains 1,000 mg of pemetrexed (as pemetrexed disodium hemipentahydrate).

After reconstitution, the solution contains 25 mg/ml of pemetrexed.
The other ingredients are mannitol, hydrochloric acid and sodium hydroxide, please see section 2 “Pemetrexed medac contains sodium”.

What Pemetrexed medac looks like and contents of the pack
Pemetrexed medac is a powder for concentrate for solution for infusion in a glass vial with rubber stopper.

Medicinal product no longer authorised

It is a white to light yellow powder.

Each pack consists of one vial containing 100, 500 or 1,000 mg of pemetrexed.

Marketing Authorisation Holder
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This leaflet was last revised in {MM/YYYY}.

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

The following information is intended for healthcare professionals only:

Instructions for use, handling and disposal

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

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

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

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

Pemetrexed medac 1,000 mg:
Reconstitute each 1,000 mg vial with 40 ml of 9 mg/ml (0.9 %) sodium chloride 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 yellow or green-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 9 mg/ml (0.9 %) sodium chloride 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 should 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 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 a 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.

Medicinal product no longer authorised

Annex IV
Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Medicinal product no longer authorised

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for pemetrexed, the scientific conclusions of PRAC are as follows:

In view of available data on the pharmacokinetics of pemetrexed and considering *in vitro* studies indicated that pemetrexed is actively secreted by organic anion transporter 3 (OAT3) and IC50 values for proton pump inhibitors, the PRAC considers a drug-drug interaction between proton pump inhibitors and pemetrexed is at least a reasonable possibility. The PRAC concluded that the product information of products containing pemetrexed should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for pemetrexed the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing pemetrexed is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.

Medicinal product no longer authorised