

# ALIMTA

## Pemetrexed

### 1. NAME OF THE MEDICINAL PRODUCT

ALIMTA 100 mg powder for concentrate for solution for infusion  
ALIMTA 500 mg powder for concentrate for solution for infusion

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ALIMTA 100 mg powder for concentrate for solution for infusion  
Each vial contains 100 mg of pemetrexed (as pemetrexed disodium).

*Excipient with known effect*  
Each vial contains approximately 11 mg sodium.

ALIMTA 500 mg powder for concentrate for solution for infusion  
Each vial contains 500 mg of pemetrexed (as pemetrexed disodium).

*Excipient with known effect*  
Each vial contains approximately 54 mg sodium.

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

For the full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.  
White to either light yellow or green-yellow lyophilised powder.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

*Malignant Pleural Mesothelioma:*

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

*Non-small cell lung cancer:*

ALIMTA 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).

ALIMTA 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. First line treatment should be a platinum based with other cytotoxics chemotherapy (see section 5.1).

ALIMTA is indicated as a single-agent for the treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer after prior chemotherapy (as second line).

ALIMTA is not indicated for treatment of patients with squamous cell non-small cell lung cancer.

## 4.2 Posology and method of administration

### Posology

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

#### *ALIMTA in combination with cisplatin*

The recommended dose of ALIMTA is 500 mg/m<sup>2</sup> 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<sup>2</sup> 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).

#### *ALIMTA as single agent*

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

#### *Pre-medication regimen*

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

To reduce toxicity, patients treated with pemetrexed must also receive vitamin supplementation (see section 4.4). Patients must take oral folic acid or a multivitamin containing folic acid (350 to 1000 micrograms) on a daily basis. At least five doses of folic acid must be taken during the seven days preceding the first dose of pemetrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients must also receive an intramuscular injection of vitamin B<sub>12</sub> (1000 micrograms) in the week preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B<sub>12</sub> 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  $\geq 1500$  cells/mm<sup>3</sup> and platelets should be  $\geq 100,000$  cells/mm<sup>3</sup>. Creatinine clearance should be  $\geq 45$  mL/min.

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

**Dose adjustments**

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

<b>Table 1 – Dose modification table for ALIMTA (as single agent or in combination) and cisplatin – Haematologic toxicities</b>	
Nadir ANC < 500 /mm <sup>3</sup> and nadir platelets ≥ 50,000 /mm <sup>3</sup>	75 % of previous dose (both ALIMTA and cisplatin)
Nadir platelets <50,000 /mm <sup>3</sup> regardless of nadir ANC	75 % of previous dose (both ALIMTA and cisplatin)
Nadir platelets <50,000/mm <sup>3</sup> with bleeding <sup>a</sup> , regardless of nadir ANC	50% of previous dose (both ALIMTA and cisplatin)

<sup>a</sup> 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), ALIMTA 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.

<b>Table 2 - Dose modification table for ALIMTA (as single agent or in combination) and cisplatin– Non-haematologic toxicities <sup>a, b</sup></b>		
	<b>Dose of ALIMTA (mg/m<sup>2</sup>)</b>	<b>Dose for cisplatin (mg/m<sup>2</sup>)</b>
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 <sup>a</sup>	75 % of previous dose	75 % of previous dose
Grade 3 or 4 mucositis	50 % of previous dose	100 % of previous dose

<sup>a</sup> National Cancer Institute Common Toxicity Criteria (CTC v2.0; NCI 1998) <sup>b</sup> Excluding neurotoxicity

In the event of neurotoxicity, the recommended dose adjustment for ALIMTA and cisplatin is documented in Table 3. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is observed

<b>Table 3 - Dose modification table for ALIMTA (as single agent or in combination) and cisplatin – Neurotoxicity</b>		
<b>CTC<sup>a</sup> Grade</b>	<b>Dose of ALIMTA (mg/m<sup>2</sup>)</b>	<b>Dose for cisplatin (mg/m<sup>2</sup>)</b>
0 – 1	100 % of previous dose	100 % of previous dose

2	100 % of previous dose	50 % of previous dose
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<sup>a</sup> National Cancer Institute Common Toxicity Criteria (CTC v2.0; NCI 1998)

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

### Special populations

#### *Elderly*

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

#### *Paediatric population*

ALIMTA is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy.

#### *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  $\geq 45$  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

ALIMTA is for intravenous use. ALIMTA 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 ALIMTA and for instructions on reconstitution and dilution of ALIMTA 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 must be discontinued during pemetrexed therapy (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  $\geq 1500$  cells/mm<sup>3</sup> and platelet count returns

to  $\geq 100,000$  cells/mm<sup>3</sup>. 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<sub>12</sub> was administered. Therefore, all patients treated with pemetrexed must be instructed to take folic acid and vitamin B<sub>12</sub> as a prophylactic measure to reduce treatment-related toxicity (see section 4.2).

Skin reactions have been reported in patients not pre-treated with a corticosteroid. Pre-treatment with dexamethasone (or equivalent) can reduce the incidence and severity of skin reactions (see section 4.2).

An insufficient number of patients has been studied with creatinine clearance of below 45 mL/min. Therefore, the use of pemetrexed in patients with creatinine clearance of < 45 mL/min is not recommended (see section 4.2).

Patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min) should avoid taking non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, and acetylsalicylic acid (> 1.3 g daily) for 2 days before, on the day of, and 2 days following pemetrexed administration (see section 4.5).

In patients with mild to moderate renal insufficiency eligible for pemetrexed therapy NSAIDs with long elimination half-lives should be interrupted for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration (see section 4.5).

Serious renal events, including acute renal failure, have been reported with pemetrexed alone or in association with other chemotherapeutic agents. Many of the patients in whom these occurred had underlying risk factors for the development of renal events including dehydration or pre-existing hypertension or diabetes. Nephrogenic diabetes insipidus and renal tubular necrosis were also reported in post marketing setting with pemetrexed alone or with other chemotherapeutic agents. Most of these events resolved after pemetrexed withdrawal. Patients should be regularly monitored for acute tubular necrosis, decreased renal function and signs and symptoms of nephrogenic diabetes insipidus (e.g. hypernatraemia).

The effect of third space fluid, such as pleural effusion or ascites, on pemetrexed is not fully defined. A phase 2 study of pemetrexed in 31 solid tumour patients with stable third space fluid demonstrated no difference in pemetrexed dose normalized plasma concentrations or clearance compared to patients without third space fluid collections. Thus, drainage of third space fluid collection prior to pemetrexed treatment should be considered, but may not be necessary.

Due to the gastrointestinal toxicity of pemetrexed given in combination with cisplatin, severe dehydration has been observed. Therefore, patients should receive adequate antiemetic treatment and appropriate hydration prior to and/or after receiving treatment.

Serious cardiovascular events, including myocardial infarction and cerebrovascular events have been uncommonly reported during clinical studies with pemetrexed, usually when given in combination with another cytotoxic agent. Most of the patients in whom these events have been observed had preexisting cardiovascular risk factors (see section 4.8).

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

Pemetrexed can have genetically damaging effects. Sexually mature males are advised not to father a child during the treatment and up to 6 months thereafter. Contraceptive measures or abstinence are recommended. Owing to the possibility of pemetrexed treatment causing irreversible infertility, men are advised to seek counselling on sperm storage before starting treatment.

Women of childbearing potential must use effective contraception during treatment with pemetrexed (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

#### ALIMTA 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'.

#### ALIMTA 500 mg powder for concentrate for solution for infusion

This medicinal product contains 54 mg of sodium per vial, equivalent to 2,7 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

### **4.5 Interaction with other medicinal products and other forms of interaction**

Pemetrexed is mainly eliminated unchanged renally by tubular secretion and to a lesser extent by glomerular filtration. Concomitant administration of nephrotoxic drugs (e.g. aminoglycoside, loop diuretics, platinum compounds, cyclosporin) could potentially result in delayed clearance of pemetrexed. This combination should be used with caution. If necessary, creatinine clearance should be closely monitored.

Concomitant administration of substances that are also tubularly secreted (e.g. probenecid, penicillin) could potentially result in delayed clearance of pemetrexed. Caution should be made when these drugs are combined with pemetrexed. If necessary, creatinine clearance should be closely monitored.

In patients with normal renal function (creatinine clearance  $\geq 80$  mL/min), high doses of non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen  $> 1600$  mg/day) and acetylsalicylic acid at higher dose ( $\geq 1.3$  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  $\geq 80$  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, 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).

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

#### Interactions common to all cytotoxics

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

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

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

### **4.6 Fertility, pregnancy and lactation**

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

Women of childbearing potential must use effective contraception during treatment with pemetrexed. Pemetrexed can have genetically damaging effects. Sexually mature males are advised not to father a child during the treatment and up to 6 months thereafter. Contraceptive measures or abstinence are recommended.

#### 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.

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:  $\geq 1/10$ ; common:  $\geq 1/100$  to  $< 1/10$ ; uncommon:  $\geq 1/1,000$  to  $< 1/100$ ; rare:  $\geq 1/10,000$  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 <sup>a</sup> Pharyngitis	Sepsis <sup>b</sup>			Dermo-hypodermi tis	
Blood and lymphatic system disorders	Neutropenia Leukopenia Haemoglobin decreased	Febrile neutropenia 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 Peripheral motor neuropathy Peripheral sensory neuropathy Dizziness	Cerebrovasc ular accident Ischaemic stroke Haemorrhag e intracranial			
Eye disorders		Conjunctivitis Dry eye				

		Lacrimation increased Keratoconjunctivitis sicca Eyelid oedema Ocular surface disease				
Cardiac disorders		Cardiac failure Arrhythmia	Angina Myocardial infarction  Coronary artery disease Arrhythmia supraventricular			
Vascular disorders			Peripheral ischaemia <sup>c</sup>			
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism Interstitial pneumonitis <sup>bd</sup>			
Gastrointestinal disorders	Stomatitis Anorexia Vomiting Diarrhoea Nausea	Dyspepsia Constipation Abdominal pain	Rectal haemorrhage Gastrointestinal haemorrhage Intestinal perforation Oesophagitis Colitis <sup>e</sup>			
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 <sup>b</sup> Toxic epidermal necrolysis <sup>b</sup> Pemphigoid Dermatitis bullous	

					Acquired epidermolysis bullosa Erythematous oedema <sup>f</sup> Pseudocellulitis Dermatitis Eczema Prurigo	
Renal and urinary disorders	Creatinine clearance decreased Blood creatinine increased <sup>e</sup>	Renal failure Glomerular filtration rate decreased				Nephrogenic diabetes insipidus  Renal tubular necrosis
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		

<sup>a</sup> with and without neutropenia

<sup>b</sup> in some cases fatal

<sup>c</sup> sometimes leading to extremity necrosis

<sup>d</sup> with respiratory insufficiency

<sup>e</sup> seen only in combination with cisplatin

<sup>f</sup> 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.

#### **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

ALIMTA (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 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.

#### Clinical efficacy

##### *Mesothelioma*

EMPHACIS, a multicentre, randomised, single-blind phase 3 study of ALIMTA plus cisplatin versus cisplatin in chemo-naïve patients with malignant pleural mesothelioma, has shown that patients treated with ALIMTA 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<sub>12</sub> 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<sub>12</sub> 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 ALIMTA plus cisplatin vs. cisplatin in malignant pleural mesothelioma**

Efficacy parameter	Randomized and treated patients		Fully supplemented patients	
	ALIMTA/ cisplatin (N=226)	Cisplatin (N=222)	ALIMTA/ cisplatin (N=168)	Cisplatin (N=163)
Median overall survival (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 <sup>a*</sup>	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 <sup>a*</sup>	0.001		0.001	
Overall response rate <sup>b**</sup> (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 <sup>a*</sup>	<0.001	<0.001
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Abbreviation: CI = confidence interval

<sup>a\*</sup> p-value refers to comparison between arms.

<sup>b\*\*</sup> In the ALIMTA/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 ALIMTA/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 ALIMTA/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 ALIMTA alone. ALIMTA at a dose of 500 mg/m<sup>2</sup> was studied as a single-agent in 64 chemo-naïve patients with malignant pleural mesothelioma. The overall response rate was 14.1 %.

*NSCLC, second-line treatment*

A multicentre, randomised, open label phase 3 study of ALIMTA 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 ALIMTA (Intent To Treat population n = 283) and 7.9 months for patients treated with docetaxel (ITT n = 288).

An analysis of the impact of NSCLC histology on the treatment effect on overall survival was in favour of ALIMTA versus docetaxel for other than predominantly squamous histologies (n = 399, 9.3 versus 8.0 months, adjusted 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 ALIMTA within the histology subgroups.

Limited clinical data from a separate randomized, 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 ALIMTA vs docetaxel in NSCLC - ITT population**

	<b>ALIMTA</b>	<b>Docetaxel</b>
<b>Survival Time (months)</b>	(n=283)	(n=288)
▪ <b>Median (m)</b>	8.3	7.9
▪ <b>95% CI for median</b>	(7.0 – 9.4)	(6.3 – 9.2)
▪ <b>HR</b>		0.99
▪ <b>95% CI for HR</b>		(.82 - 1.20)
▪ <b>Non-inferiority p-value (HR)</b>		.226
<b>Progression free survival (months)</b>	(n = 283)	(n = 288)
▪ <b>Median</b>	2.9	2.9
▪ <b>HR (95% CI)</b>		0.97 (.82 – 1.16)
<b>Time to treatment failure (TTTF – months)</b>	(n = 283)	(n = 288)
▪ <b>Median</b>	2.3	2.1
▪ <b>HR (95% CI)</b>		0.84 (.71 - .997)

<b>Response (n: qualified for response)</b>	(n = 264)	(n = 274)
▪ <b>Response rate (%) (95% CI)</b>	9.1 (5.9 - 13.2)	8.8 (5.7 - 12.8)
▪ <b>Stable disease (%)</b>	45.8	46.4

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent to treat; n = total population size.

#### NSCLC, first-line treatment

A multicentre, randomised, open-label, Phase 3 study of ALIMTA plus cisplatin versus gemcitabine plus cisplatin in chemo-naïve patients with locally advanced or metastatic (Stage IIIb or IV) non-small cell lung cancer (NSCLC) showed that ALIMTA 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 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 ALIMTA 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 ALIMTA 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.

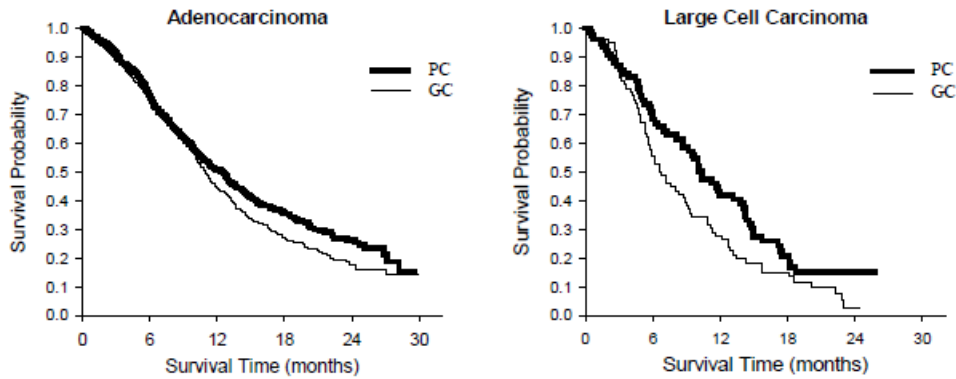
**Table 7. Efficacy of ALIMTA + cisplatin vs. gemcitabine + cisplatin in first-line non-small cell lung cancer – ITT population and histology subgroups.**

ITT population and histology subgroups	Median overall survival in months (95% CI)		Adjusted hazard ratio (HR) (95% CI)	Superiority p-value
	ALIMTA + 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 <sup>a</sup> (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

<sup>a</sup> 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 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 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) 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  $\geq 6$  cycles and a total of 103 patients (23.4 %) completed  $\geq 10$  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,  $p = 0.01192$ ).

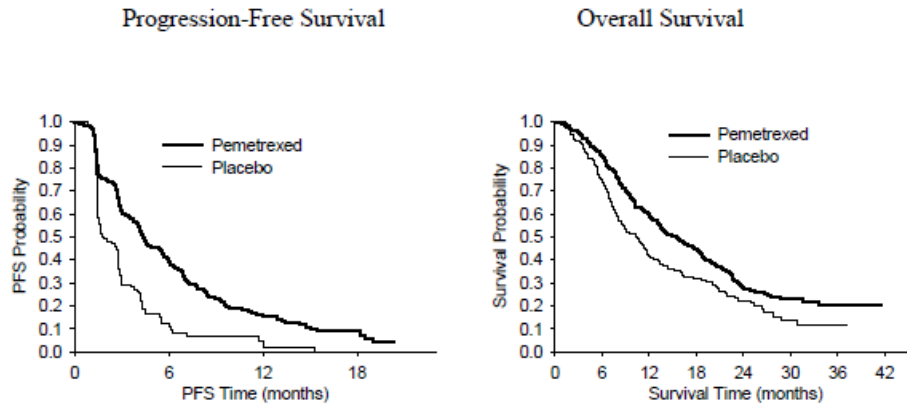
Consistent with other pemetrexed studies, a difference in efficacy according to NSCLC histology was observed in JMEN. For patients with NSCLC other than predominantly squamous cell histology ( $n = 430$ , independently reviewed population) median PFS was 4.4 months for the pemetrexed arm and 1.8 months 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:**



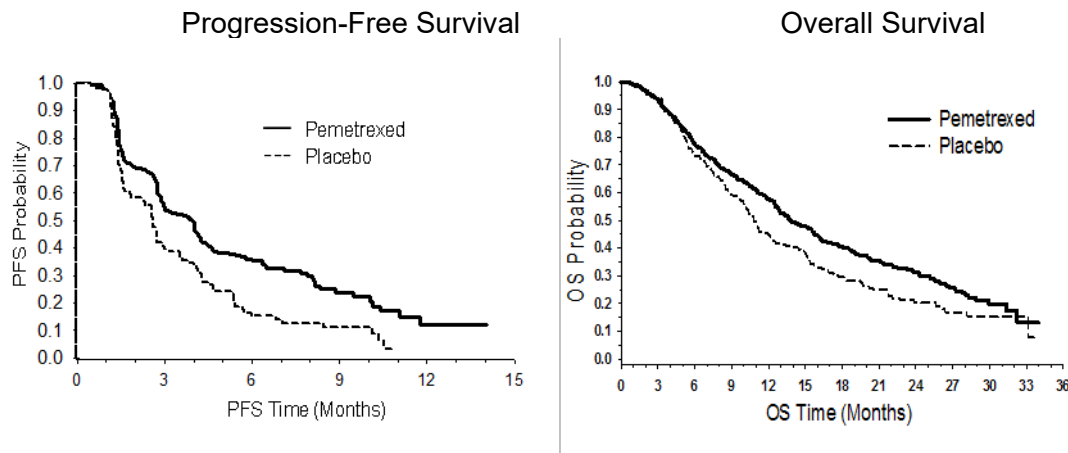
**PARAMOUNT**

A 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 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 109 patients (30.4 %) 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 ALIMTA plus cisplatin induction (4 cycles), treatment with ALIMTA 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 ALIMTA arm versus 21.7% on the placebo arm. The relative treatment effect of ALIMTA 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 ALIMTA were 58% and 32% respectively, compared to 45% and 21% for patients on placebo. From the start of ALIMTA plus cisplatin first line induction treatment, the median OS of patients was 16.9 months for the ALIMTA 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 ALIMTA and 71.7% for placebo.

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



The ALIMTA 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<sup>2</sup> infused over a 10-minute period. Pemetrexed has a steady-state volume of distribution of 9 L/m<sup>2</sup>. *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. 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 B12 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.

#### Reconstituted and infusion solution

When prepared as directed, reconstituted and infusion solutions of Alimta 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**

Store below 30°C.

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

### **6.5 Nature and contents of container**

#### Alimta 100 mg powder for concentrate for solution for infusion

Type I glass vial with rubber stopper containing 100 mg of pemetrexed.

Pack of 1 vial.

### Alimta 500 mg powder for concentrate for solution for infusion

Type I glass vial with rubber stopper containing 500 mg of pemetrexed.  
Pack of 1 vial.

#### **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 Alimta vials needed. Each vial contains an excess of pemetrexed to facilitate delivery of label amount.

3. Alimta 100 mg powder for concentrate for solution for infusion 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. Alimta 500 mg powder for concentrate for solution for infusion

Alimta 500 mg powder for concentrate for solution for infusion: 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 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 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.

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.

#### **6.7 Presentation**

Alimta 100 mg; Box of 1 vial. Reg. No.: DK12188802880A1

Alimta 500 mg; Box of 1 vial. Reg. No.: DK12188802880B1

**HARUS DENGAN RESEP DOKTER**

Manufactured by:  
Vianex S.A. – Plant C  
Pallini Attiki – Greece

Packed and released by:  
Lilly France  
Fegersheim - France

Registered by:  
PT Pyridam Farma Tbk.  
Kabupaten Cianjur, Indonesia.

## Informasi Produk untuk Pasien

Alimta serbuk injeksi 100mg  
Alimta serbuk injeksi 500mg

### Pemetrexed

Bacalah seluruh leaflet ini dengan seksama sebelum mulai penggunaan obat ini karena obat ini mengandung informasi penting untuk Anda.

- Simpanlah leaflet ini, agar dapat dibaca kembali jika diperlukan
- Jika ada pertanyaan lebih lanjut, hubungilah dokter atau apoteker
- Obat ini diresepkan untuk Anda. Jangan diberikan kepada orang lain. Hal tersebut dikarenakan obat ini dapat saja membahayakan orang lain, walaupun gejala yang dialami sama dengan Anda
- Jika salah satu efek samping dirasakan menjadi serius atau jika terjadi efek samping apapun yang tidak tercantum di leaflet ini, mohon sampaikan kepada dokter atau apoteker

Pada leaflet ini terdapat informasi berikut:

1. Apakah ALIMTA dan kegunaannya
2. Hal yang harus diperhatikan sebelum pemberian ALIMTA
3. Bagaimana cara ALIMTA diberikan
4. Kemungkinan efek samping yang terjadi
5. Bagaimana cara menyimpan ALIMTA
6. Informasi lainnya

#### 1. APAKAH ALIMTA DAN KEGUNAANNYA

ALIMTA adalah obat yang digunakan untuk mengobati penyakit kanker.

ALIMTA diberikan dalam kombinasi dengan cisplatin, obat anti kanker lainnya, sebagai pengobatan untuk *malignant pleural mesothelioma*, jenis kanker yang mempengaruhi lapisan paru-paru, kepada pasien yang belum menerima kemoterapi sebelumnya.

ALIMTA juga diberikan dalam kombinasi dengan cisplatin untuk pengobatan lini pertama pada pasien kanker paru-paru stadium lanjut.

ALIMTA dapat diresepkan pada kanker paru-paru stadium lanjut yang penyakitnya telah memberikan respon atau cenderung tidak ada perubahan terhadap pengobatan kemoterapi awalnya.

ALIMTA juga merupakan pengobatan pada pasien kanker paru-paru yang penyakitnya telah mengalami kemajuan setelah pengobatan kemoterapi sebelumnya selesai.

#### 2. HAL YANG HARUS DIPERHATIKAN SEBELUM PEMBERIAN ALIMTA

**ALIMTA tidak boleh diberikan pada keadaan berikut:**

- Alergi (hipersensitif) terhadap pemetrexed atau komposisi lain dari obat ini (lihat bagian 6)
- Menyusui; selama pengobatan dengan ALIMTA kegiatan menyusui harus dihentikan
- Baru saja atau akan melakukan vaksinasi demam kuning

#### Peringatan dan perhatian

**Beritahukan dokter atau apoteker di rumah sakit Anda sebelum menggunakan Alimta.**

Jika sedang atau sebelumnya memiliki masalah dengan ginjal, sampaikanlah kepada dokter atau apoteker rumah sakit karena ada kemungkinan ALIMTA tidak dapat diberikan.

Sebelum diinfus, sampel darah akan diambil untuk diperiksa apakah fungsi ginjal dan paru-paru cukup baik dan untuk mengecek apakah terdapat cukup sel darah untuk menerima ALIMTA. Dokter akan dapat memutuskan untuk mengubah atau menunda pemberian ALIMTA tergantung kepada kondisi umum kesehatan dan jika jumlah sel darah terlalu rendah. Jika sedang menerima cisplatin juga, maka dokter akan memastikan bahwa hidrasi dilakukan dengan tepat dan juga dilakukan perawatan sebelum dan sesudah pemberian cisplatin untuk mencegah muntah.

Jika pernah atau akan menjalani terapi radiasi, sampaikan kepada dokter, karena mungkin akan terjadi reaksi awal atau lambat radiasi dengan ALIMTA.

Jika baru saja mendapatkan vaksinasi, sampaikan kepada dokter, karena hal ini dapat menyebabkan efek buruk terhadap ALIMTA.

Jika memiliki penyakit jantung atau sejarah penyakit tersebut, sampaikan kepada dokter.

Jika terdapat akumulasi cairan di sekitar paru-paru, dokter akan memutuskan untuk mengeluarkan cairan tersebut terlebih dahulu sebelum memberikan ALIMTA.

### **Anak-anak dan remaja**

Obat ini tidak boleh digunakan untuk anak-anak dan remaja, karena tidak ada pengalaman penggunaan obat ini pada anak-anak dan remaja di bawah 18 tahun.

### **Pemberian obat-obatan lainnya**

Sampaikan kepada dokter jika sedang mengonsumsi obat untuk nyeri atau inflamasi (pembengkakan), seperti obat-obatan yang disebut "obat anti-inflamasi nonsteroid (AINS)", termasuk obat yang dibeli tanpa menggunakan resep dokter (misalnya ibuprofen). AINS ini terdapat banyak jenisnya dengan durasi kerja yang berbeda-beda. Berdasarkan rencana pelaksanaan infus ALIMTA dan/atau status fungsi ginjal, dokter akan memberikan nasihat mengenai obat manakah untuk diminum dan kapan meminumnya. Jika ragu, maka tanyakan kepada dokter atau apoteker apakah terdapat obat-obat AINS di antara obat yang sedang dikonsumsi.

Sampaikan kepada dokter atau apoteker rumah sakit jika sedang atau baru saja mengonsumsi obat-obatan lain, termasuk obat yang didapatkan tanpa resep (obat bebas).

### **Kehamilan**

Jika sedang hamil atau kemungkinan akan hamil, sampaikan kepada dokter. Penggunaan ALIMTA harus dihindarkan selama kehamilan. Dokter akan mendiskusikan potensi resiko menggunakan ALIMTA selama kehamilan. Pasien perempuan harus menggunakan kontrasepsi yang efektif selama pengobatan menggunakan ALIMTA.

### **Menyusui**

Jika sedang menyusui, sampaikan kepada dokter. Proses menyusui harus dihentikan selama pengobatan dengan ALIMTA.

### **Kesuburan**

Pasien pria disarankan untuk tidak memiliki anak selama pengobatan dan 6 bulan setelahnya, oleh karena itu harus menggunakan kontrasepsi yang efektif selama itu. Jika ingin memiliki anak selama perawatan atau dalam jangka waktu 6 bulan setelahnya, mintalah nasihat dari dokter atau apoteker. Konseling mengenai penyimpanan sel sperma juga patut untuk dipertimbangkan sebelum memulai pengobatan.

### **Mengemudi dan mengoperasikan mesin**

ALIMTA dapat menyebabkan rasa lelah. Harap berhati-hati jika mengendarai mobil atau mengoperasikan suatu mesin.

**ALIMTA mengandung natrium**

ALIMTA 100 mg serbuk injeksi

Obat ini mengandung kurang dari 1 mmol natrium (23 mg) per vial, pada dasarnya “bebas natrium”.

ALIMTA 500 mg serbuk injeksi

Obat ini mengandung kurang lebih 54 mg natrium (komponen utama garam dapur) dalam setiap vial. Ini setara dengan 2,7% dari asupan natrium harian maksimum yang direkomendasikan untuk orang dewasa.

**3. BAGAIMANA CARA ALIMTA DIBERIKAN**

Dosis ALIMTA adalah 500 miligram untuk setiap meter persegi area permukaan tubuh. Tinggi dan berat badan akan diukur untuk mengetahui area permukaan tubuh. Kemudian, dokter akan menggunakan data area permukaan tubuh ini untuk menentukan dosis yang tepat. Dosis ini dapat disesuaikan, atau pengobatan akan ditunda tergantung kepada jumlah sel darah dan kondisi umum kesehatan tubuh. Apoteker rumah sakit, perawat atau dokter akan mencampur serbuk ALIMTA dengan 9 mg/ml (0.9%) larutan natrium klorida untuk injeksi sebelum diberikan.

ALIMTA akan selalu diberikan melalui infus ke dalam salah satu pembuluh darah vena. Proses infus ini akan berlangsung selama kurang lebih 10 menit.

Ketika menggunakan ALIMTA dikombinasikan dengan cisplatin:

Dokter atau apoteker rumah sakit akan menentukan dosis yang dibutuhkan berdasarkan tinggi dan berat badan. Cisplatin juga diberikan melalui infus ke salah satu pembuluh darah vena kurang lebih 30 menit setelah infus ALIMTA selesai. Infus cisplatin ini diberikan selama kurang lebih 2 jam.

Infus biasanya diberikan sekali setiap 3 minggu.

Obat-obatan tambahan:

Kortikosteroid: dokter akan meresepkan tablet steroid (setara dengan 4 miligram deksametason dua kali sehari) yang harus diminum sehari sebelum, pada saat dan sehari sesudah pemberian ALIMTA. Obat ini diberikan untuk mengurangi frekuensi dan tingkat keparahan dari reaksi pada kulit yang mungkin akan muncul selama pengobatan menggunakan antikanker.

Suplemen vitamin: dokter akan meresepkan asam folat oral (vitamin) atau multivitamin yang mengandung asam folat (350-1000 microgram) yang harus diminum sehari sekali selama penggunaan ALIMTA. Vitamin ini harus diminum minimal selama 7 hari sebelum dosis ALIMTA pertama kali diberikan. Kemudian, harus dilanjutkan selama 21 hari sesudah dosis terakhir ALIMTA. Injeksi vitamin B12 (1000 microgram) juga akan diberikan seminggu sebelum pemberian ALIMTA dan kemudian kurang lebih 9 minggu (terkait dengan 3 kali pemberian ALIMTA). Vitamin B12 dan asam folat diberikan untuk mengurangi kemungkinan efek toksik dari pengobatan antikanker.

Jika ada pertanyaan lebih lanjut mengenai penggunaan obat ini, tanyakan kepada dokter atau apoteker.

**4. KEMUNGKINAN EFEK SAMPING YANG TERJADI**

Seperti halnya obat-obatan lainnya, ALIMTA dapat menyebabkan efek samping, walaupun tidak semua orang akan mengalaminya.

Segera hubungi dokter jika mendapati hal berikut:

- Demam atau infeksi (berturut-turut, umum terjadi atau sangat umum terjadi): jika suhu tubuh mencapai 38°C atau lebih, berkeringat atau pertanda lain dari infeksi (karena jumlah sel darah putih menjadi lebih sedikit daripada jumlah normal yang mana hal tersebut adalah umum terjadi). Infeksi (sepsis) dapat menjadi parah dan mengakibatkan kematian.
- Jika mulai terasa sakit di bagian dada (umum terjadi) atau detak jantung menjadi cepat (tidak umum terjadi).
- Jika mengalami rasa sakit, kemerahan, pembengkakan atau radang di mulut (sangat umum terjadi)
- Reaksi alergi: jika terjadi kemerahan di kulit (sangat umum terjadi)/ rasa terbakar atau tertusuk-tusuk (umum terjadi), atau demam (umum terjadi). Reaksi pada kulit ini dapat menjadi parah dan menyebabkan kematian, meski jarang terjadi. Hubungi dokter jika muncul kemerahan yang parah atau rasa gatal atau melepuh (*Stevens-Johnson Syndrome* atau *toxic epidermal necrolysis*).
- Jika mengalami kelelahan, nyaris pingsan, menjadi mudah terengah-engah atau nampak pucat (hal tersebut dikarenakan lebih rendahnya kadar hemoglobin darah dari kadar normal, yang mana ini adalah sangat umum terjadi).
- Jika mengalami pendarahan dari gusi, hidung atau mulut atau pendarahan lainnya yang tidak berhenti, urin berwarna kemerahan atau merah muda, memar tanpa sebab (hal tersebut dikarenakan jumlah platelet darah yang mungkin lebih sedikit daripada keadaan normal, yang mana ini adalah umum terjadi).
- Jika mengalami sesak nafas mendadak, sakit bagian dada yang hebat atau batuk berdarah disertai darah (tidak umum terjadi) (hal tersebut dapat merupakan pertanda adanya darah beku pada pembuluh darah paru-paru)

Efek samping ALIMTA dapat berupa:

*Sangat umum terjadi (dapat mempengaruhi lebih dari 1 dari 10 orang)*

Infeksi

*Faringitis* (sakit tenggorokan)

Jumlah granulosit neutrofil yang rendah (sejenis sel darah putih)

Sel darah putih rendah

Kadar hemoglobin rendah

Rasa nyeri, kemerahan, bengkak atau luka di mulut Anda

Kehilangan selera makan

Muntah

Diare

Mual

Ruam kulit

Kulit mengelupas

Tes darah abnormal menunjukkan penurunan fungsi ginjal

Kelelahan

*Umum terjadi (dapat mempengaruhi hingga 1 dari 10 orang)*

Infeksi darah

Demam dengan jumlah granulosit neutrofil yang rendah (sejenis sel darah putih)

Jumlah trombosit rendah

Reaksi alergi

Kehilangan cairan tubuh

Perubahan rasa

Kerusakan pada saraf motorik yang dapat menyebabkan kelemahan otot dan atrofi primer pada lengan dan kaki)

Kerusakan pada saraf sensorik yang dapat menyebabkan hilangnya sensasi, rasa sakit yang membakar dan gaya berjalan yang goyah

Pusing

Peradangan atau pembengkakan konjungtiva (selaput yang melapisi kelopak mata dan menutupi bagian putih mata)  
Mata kering  
Mata berair  
Kekeringan pada konjungtiva (selaput yang melapisi kelopak mata dan menutupi bagian putih mata) dan kornea (lapisan bening di depan iris dan pupil).  
Pembengkakan kelopak mata  
Gangguan mata dengan kekeringan, robek, iritasi, dan/atau nyeri  
Gagal Jantung (Kondisi yang mempengaruhi daya pompa otot jantung Anda)  
Irama jantung tidak teratur  
Gangguan pencernaan  
Sembelit  
Sakit perut  
Hati: peningkatan bahan kimia dalam darah yang dibuat oleh hati  
Pigmentasi kulit meningkat  
Kulit yang gatal  
Ruam di tubuh di mana setiap tanda menyerupai *bullseye*  
Rambut rontok  
Gatal-gatal  
Ginjal berhenti bekerja  
Berkurangnya fungsi ginjal  
Demam  
Nyeri  
Kelebihan cairan dalam jaringan tubuh, menyebabkan pembengkakan  
Sakit dada  
Peradangan dan ulserasi pada selaput lendir yang melapisi saluran pencernaan

*Tidak umum terjadi (dapat mempengaruhi hingga 1 dari 100 orang)*

Pengurangan jumlah sel darah merah, sel darah putih dan trombosit  
Stroke  
Jenis stroke ketika arteri ke otak tersumbat  
Pendarahan di dalam tengkorak  
Angina (nyeri dada yang disebabkan oleh berkurangnya aliran darah ke jantung)  
Serangan jantung  
Penyempitan atau penyumbatan arteri koroner  
Ritme jantung meningkat  
Distribusi darah yang kurang ke anggota badan  
Penyumbatan di salah satu arteri pulmonalis di paru-paru Anda  
Peradangan dan jaringan parut pada lapisan paru-paru dengan masalah pernapasan  
Keluarnya darah merah cerah dari anus  
Pendarahan di saluran pencernaan  
Usus pecah  
Peradangan pada lapisan kerongkongan  
Peradangan pada lapisan usus besar, yang mungkin disertai dengan pendarahan usus atau dubur (hanya terlihat dalam kombinasi dengan cisplatin)  
Peradangan, edema, eritema, dan erosi permukaan mukosa kerongkongan yang disebabkan oleh terapi radiasi  
Peradangan paru-paru yang disebabkan oleh terapi radiasi

*Jarang terjadi (dapat mempengaruhi hingga 1 dari 1.000 orang)*

Penghancuran sel darah merah  
Syok anafilaksis (reaksi alergi parah)  
Kondisi peradangan hati  
Kemerahan pada kulit  
Ruam kulit yang berkembang di seluruh area yang sebelumnya diiradiasi

*Sangat jarang terjadi (mempengaruhi hingga 1 dari 10.000 orang)*

Infeksi kulit dan jaringan lunak

Sindrom Stevens-Johnson (sejenis reaksi kulit dan selaput lendir yang parah yang dapat mengancam jiwa)

Nekrolisis epidermal toksik (sejenis reaksi kulit parah yang dapat mengancam jiwa)

Gangguan autoimun yang menyebabkan ruam kulit dan melepuh pada kaki, lengan, dan perut

Peradangan pada kulit yang ditandai dengan adanya bula yang berisi cairan

Kerapuhan kulit, lecet dan erosi dan jaringan parut kulit

Kemerahan, nyeri dan pembengkakan terutama pada tungkai bawah

Peradangan pada kulit dan lemak di bawah kulit (pseudocellulitis)

Peradangan pada kulit (dermatitis)

Kulit menjadi meradang, gatal, merah, pecah-pecah, dan kasar

Bintik-bintik yang sangat gatal

*Tidak diketahui: frekuensi tidak dapat diperkirakan dari data yang tersedia*

Bentuk diabetes terutama karena patologi ginjal

Gangguan ginjal yang melibatkan kematian sel epitel tubulus yang membentuk tubulus ginjal

Semua gejala/kondisi tersebut di atas memiliki kemungkinan untuk terjadi. Hubungilah dokter sesegera mungkin ketika mulai mengalami gejala manapun.

Jika merasakan adanya efek samping, sampaikan kepada dokter.

#### **Pelaporan efek samping**

Jika Anda mengalami efek samping, sampaikan kepada dokter atau apoteker Anda. Hal ini termasuk dengan efek samping yang tidak tertulis di leaflet ini. Anda juga dapat melaporkan efek samping secara langsung melalui sistem pelaporan nasional di <http://e-meso.pom.go.id> atau (021) 4244755 ext. 1079. Dengan melaporkan efek samping Anda dapat membantu menyediakan informasi lebih lanjut mengenai keamanan obat ini.

## **5. BAGAIMANA CARA MENYIMPAN ALIMTA**

Jauhkan obat ini dari jangkauan dan pandangan anak-anak.

Jangan gunakan obat ini setelah tanggal kadaluwarsa yang tercantum pada label vial dan karton.

Simpan obat ini di bawah suhu 30°C.

Rekonstitusi (penyiapan) dan proses infus larutan: produk ini harus digunakan dengan segera. Ketika disiapkan sesuai petunjuk, stabilitas kimia dan selama penggunaan dari larutan ini terbukti selama 24 jam pada suhu dingin (lemari es).

Obat ini untuk penggunaan tunggal saja; larutan yang tidak terpakai harus dibuang menurut peraturan yang ada.

## **6. INFORMASI LAINNYA**

### **Apa kandungan ALIMTA**

Zat aktif ALIMTA adalah pemetrexed.

ALIMTA 100 mg: setiap vial mengandung 100 miligram pemetrexed (dalam bentuk dinatrium pemetrexed)

ALIMTA 500 mg: setiap vial mengandung 500 miligram pemetrexed (dalam bentuk dinatrium pemetrexed)

Setelah rekonstitusi, larutan ALIMTA mengandung 25 mg/ml pemetrexed. Pelarutan lanjut oleh petugas kesehatan dilakukan sebelum pemberian kepada pasien. Kandungan lain ALIMTA adalah manitol, asam hidroklorida dan natrium hidroksida.

**Seperti apa wujud ALIMTA dan isiemasannya**

ALIMTA berupa serbuk untuk dilarutkan menjadi larutan infus yang dikemas dalam vial. ALIMTA merupakan serbuk terliofilisasi yang berwarna antara putih dan kuning muda atau hijau kekuningan muda.

Tersedia dalam kemasan berisi 1 vial.

**Nomor Ijin Edar**

ALIMTA 100 mg: DKI2188802880A1

ALIMTA 500 mg: DKI2188802880B1

**HARUS DENGAN RESEP DOKTER**

**Pemilik ijin edar**

PT Pyridam Farma Tbk.  
Kabupaten Cianjur, Indonesia

**Pabrik pembuat**

Vianex S.A. – Plant C  
Pallini Attiki – Yunani

**Dikemas dan dirilis oleh**

Lilly France  
Fegersheim - Perancis