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| X | Internal creator_DS_ | | Approval for Submission Date _____ | | Marketing reviewer_____ |

# ALIMTA

## Pemetrexed

### 1. NAME OF THE MEDICINAL PRODUCT

ALIMTA 500 mg powder for concentrate for solution for infusion

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

*Excipients 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$^2$ of body surface area (BSA) administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle. The recommended dose of cisplatin is 75 mg/m$^2$ BSA infused over two hours approximately 30 minutes after completion of the pemetrexed infusion on the first day of each 21-day cycle. Patients must receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving cisplatin (see also cisplatin Summary of Product Characteristics for specific dosing advice).

*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$^2$ BSA administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

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

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

*Monitoring*
Patients receiving pemetrexed should be monitored before each dose with a complete blood count, including a differential white cell count (WCC) and platelet count. Prior to each chemotherapy administration blood chemistry tests should be collected to evaluate renal and hepatic function. Before the start of any cycle of chemotherapy, patients are required to have the following: absolute neutrophil count (ANC) should be ≥ 1500 cells/mm$^3$ and platelets should be ≥ 100,000 cells/mm$^3$.
Creatinine clearance should be ≥ 45 ml/min.
The total bilirubin should be ≤ 1.5 times upper limit of normal. Alkaline phosphatase (AP), aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT) should be ≤ 3 times upper limit of normal. Alkaline phosphatase, AST and ALT ≤ 5 times upper limit of normal is acceptable if liver has tumour involvement.

*Dose adjustments*

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

| **Table 1 – Dose modification table for ALIMTA (as single agent or in combination) and cisplatin – Haemotologic toxicities** | |
|---|---|
| Nadir ANC < 500 /mm$^3$ and nadir platelets ≥ 50,000 /mm$^3$ | 75 % of previous dose (both ALIMTA and cisplatin) |
| Nadir platelets <50,000 /mm$^3$ regardless of nadir ANC | 75 % of previous dose (both ALIMTA and cisplatin) |
| Nadir platelets <50,000/mm$^3$ with bleeding[a], regardless of nadir ANC | 50% of previous dose (both ALIMTA 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), 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.

| **Table 2 - Dose modification table for ALIMTA (as single agent or in combination) and cisplatin– Non-haematologic toxicities [a, b]** | | |
|---|---|---|
| | **Dose of ALIMTA (mg/m$^2$)** | **Dose for cisplatin (mg/m$^2$)** |
| Any Grade 3 or 4 toxicities except mucositis | 75 % of previous dose | 75 % of previous dose |
| Any diarrhoea requiring hospitalisation (irrespective of grade) or grade 3 or 4 diarrhoe[a] | 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 ALIMTA 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 ALIMTA (as single agent or in combination) and cisplatin – Neurotoxicity** | | |
|---|---|---|
| **CTC[a] Grade** | **Dose of ALIMTA (mg/m$^2$)** | **Dose for cisplatin (mg/m$^2$)** |
| 0 – 1 | 100 % of previous dose | 100 % of previous dose |
| 2 | 100 % of previous dose | 50 % of previous dose |

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

Treatment with 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.

*Elderly*
In clinical studies, there has been no indication that patients 65 years of age or older are at increased risk of adverse events compared to patients younger than 65 years old. 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 ≥ 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*
For Precautions to be taken before handling or administering ALIMTA, see section 6.6.
ALIMTA should be administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle. 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 ≥ 1500 cells/$mm^3$ and platelet count returns to ≥ 100,000 cells/$mm^3$. Dose reductions for subsequent cycles are based on nadir ANC, platelet count and maximum non haematologic toxicity seen from the previous cycle (see section 4.2).

Less toxicity and reduction in Grade 3/4 haematologic and non-haematologic toxicities such as neutropenia, febrile neutropenia and infection with Grade 3/4 neutropenia were reported when pre-treatment with folic acid and vitamin $B_{12}$ was administered. Therefore, all patients treated with pemetrexed must be instructed to take folic acid and vitamin $B_{12}$ as a prophylactic measure to reduce treatment-related toxicity (see section 4.2).

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

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

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

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

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

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

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

Serious cardiovascular events, including myocardial infarction and cerebrovascular events have been uncommonly reported during clinical studies with pemetrexed, usually when given in combination with another cytotoxic agent. Most of the patients in whom these events have been observed had 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, i.e. essentially 'sodium free'.

*ALIMTA 500 mg powder for concentrate for solution for infusion*
This medicinal product contains approximately 54 mg of sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

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

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

In patients with normal renal function (creatinine clearance > 80 mL/min), high doses of non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen > 1600 mg/day) and acetylsalicylic acid at higher dose (> 1.3 g daily) may decrease pemetrexed elimination and, consequently, increase the occurrence of pemetrexed adverse events. 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, 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**
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 not known whether pemetrexed is excreted in human milk and adverse reactions on the sucklingchild 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 below provides the frequency and severity of undesirable effects that have been reported in > 5 % of 168 patients with mesothelioma who were randomised to receive cisplatin and pemetrexed and 163 patients with mesothelioma randomised to receive single agent cisplatin. In both treatment arms, these chemonaive patients were fully supplemented with folic acid and vitamin $B_{12}$.

Frequency estimate: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10,000 to <1/1000), Very rare (<1/10,000) and not known (cannot be estimated from available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

| System organ | Frequency | Event* | Pemetrexed/ cisplatin (N=168) | Cisplatin (N=163) |
|---|---|---|---|---|

| class | | | All grades toxicity (%) | Grade 3 - 4 toxicity (%) | All grades toxicity (%) | Grade 3 - 4 toxicity (%) |
|---|---|---|---|---|---|---|
| Blood and lymphatic system disorders | Very common | Neutrophils/ Granulocytes decreased | 56.0 | 23.2 | 13.5 | 3.1 |
| | | Leukocytes decreased | 53.0 | 14.9 | 16.6 | 0.6 |
| | | Haemoglobin decreased | 26.2 | 4.2 | 10.4 | 0.0 |
| | | Platelets decreased | 23.2 | 5.4 | 8.6 | 0.0 |
| Eye disorders | Common | Conjunctivitis | 5.4 | 0.0 | 0.6 | 0.0 |
| Gastrointestinal disorders | Very common | Diarrhoea | 16.7 | 3.6 | 8.0 | 0.0 |
| | | Vomiting | 56.5 | 10.7 | 49.7 | 4.3 |
| | | Stomatitis/ Pharyngitis | 23.2 | 3.0 | 6.1 | 0.0 |
| | | Nausea | 82.1 | 11.9 | 76.7 | 5.5 |
| | | Anorexia | 20.2 | 1.2 | 14.1 | 0.6 |
| | | Constipation | 11.9 | 0.6 | 7.4 | 0.6 |
| | Common | Dyspepsia | 5.4 | 0.6 | 0.6 | 0.0 |
| General disorders | Very common | Fatigue | 47.6 | 10.1 | 42.3 | 9.2 |
| Metabolism and Nutrition Disorders | Common | Dehydration | 6.5 | 4.2 | 0.6 | 0.6 |
| Nervous System Disorders | Very common | Neuropahy sensory | 10.1 | 0.0 | 9.8 | 0.6 |
| | Common | Tastes disturbance | 7.7 | 0.0*** | 6.1 | 0.0*** |
| Renal and urinary disorders | Very common | Creatinine elevation | 10.7 | 0.6 | 9.8 | 1.2 |
| | | Creatinine clearance decreased ** | 16.1 | 0.6 | 17.8 | 1.8 |
| Skin and subcutaneous tissue disorders | Very common | Rash | 16.1 | 0.6 | 4.9 | 0.0 |
| | | Alopecia | 11.3 | 0.0*** | 5.5 | 0.0*** |

*Refer to National Cancer Institute CTC version 2 for each grade of toxicity except the term "creatinine clearance decreased"
** which is derived from the term "renal/genitourinary other".
*** According to National Cancer Institute CTC (v2.0; NCI 1998), taste disturbance and alopecia should only be reported as Grade 1 or 2.

For the purpose of this table a cut off of 5 % was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed and cisplatin.

Clinically relevant CTC toxicities that were reported in ≥ 1 % and ≤ 5 % (common) of the patients that were randomly assigned to receive cisplatin and pemetrexed include: renal failure, infection, pyrexia, febrile neutropenia, increased AST, ALT, and GGT, urticaria and chest pain.
Clinically relevant CTC toxicities that were reported in < 1 % (uncommon) of the patients that were randomly assigned to receive cisplatin and pemetrexed include arrhythmia and motor neuropathy.

The table below provides the frequency and severity of undesirable effects that have been reported in > 5 % of 265 patients randomly assigned to receive single agent pemetrexed with folic acid and vitamin $B_{12}$ supplementation and 276 patients randomly assigned to receive single agent docetaxel. All patients were diagnosed with locally advanced or metastatic non-small cell lung cancer and received prior chemotherapy.

| System organ class | Frequency | Event* | Pemetrexed N = 265 | | Docetaxel N = 276 | |
|---|---|---|---|---|---|---|
| | | | All grades Toxicity (%) | Grade 3 – 4 toxicity (%) | All Grades Toxicity (%) | Grade 3 – 4 toxicity (%) |
| Blood and lymphatic system disorders | Very Common | Neutrophils/ Granulocytes decreased | 10.9 | 5.3 | 45.3 | 40.2 |
| | | Leukocytes decreased | 12.1 | 4.2 | 34.1 | 27.2 |
| | | Haemoglobin decreased | 19.2 | 4.2 | 22.1 | 4.3 |
| | Common | Platelets decreased | 8.3 | 1.9 | 1.1 | 0.4 |
| Gastrointestinal disorders | Very Common | Diarrhoea | 12.8 | 0.4 | 24.3 | 2.5 |
| | | Vomiting | 16.2 | 1.5 | 12.0 | 1.1 |
| | | Stomatitis/ Pharyngitis | 14.7 | 1.1 | 17.4 | 1.1 |
| | | Nausea | 30.9 | 2.6 | 16.7 | 1.8 |
| | | Anorexia | 21.9 | 1.9 | 23.9 | 2.5 |
| | Common | Constipation | 5.7 | 0.0 | 4.0 | 0.0 |
| General Disorders | Very Common | Fatigue | 34.0 | 5.3 | 35.9 | 5.4 |
| | Common | Fever | 8.3 | 0.0 | 7.6 | 0.0 |
| Hepatobiliary disorders | Common | SGPT (ALT) elevation | 7.9 | 1.9 | 1.4 | 0.0 |
| | | SGOT (AST) elevation | 6.8 | 1.1 | 0.7 | 0.0 |
| Skin and subcutaneous tissue disorders | Very Common | Rash/ desquamation | 14.0 | 0.0 | 6.2 | 0.0 |
| | Common | Pruritus | 6.8 | 0.4 | 1.8 | 0.0 |
| | | Alopecia | 6.4 | 0.4** | 37.7 | 2.2** |

*Refer to National Cancer Institute CTC version 2 for each grade of toxicity.

**According to National Cancer Institute CTC (v2.0; NCI 1998), alopecia should only be reported as Grade 1 or 2.

For the purpose of this table a cut off of 5 % was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed.

Clinically relevant CTC toxicities that were reported in ≥ 1 % and ≤ 5 % (common) of the patients that were randomly assigned to pemetrexed include: infection without neutropenia, febrile neutropenia, allergic reaction/hypersensitivity, increased creatinine, motor neuropathy, sensory neuropathy, erythema multiforme, and abdominal pain.

Clinically relevant CTC toxicities that were reported in < 1 % (uncommon) of the patients that were randomly assigned to pemetrexed include supraventricular arrhythmias.

Clinically relevant Grade 3 and Grade 4 laboratory toxicities were similar between integrated Phase 2 results from three single agent pemetrexed studies (n = 164) and the Phase 3 single agent pemetrexed study described above, with the exception of neutropenia (12.8 % versus 5.3 %, respectively) and alanine aminotransferase elevation (15.2 % versus 1.9 %, respectively). These differences were likely due to differences in the patient population, since the Phase 2 studies included both chemonaive and heavily pre-treated breast cancer patients with pre-existing liver metastases and/or abnormal baseline liver function tests.

The table below provides the frequency and severity of undesirable effects considered possibly related to study drug that have been reported in >5% of 839 patients with NSCLC who were randomized to receive cisplatin and pemetrexed and 830 patients with NSCLC who were randomized to receive cisplatin and gemcitabine. All patients received study therapy as initial treatment for locally advanced or metastatic NSCLC and patients in both treatment groups were fully supplemented with folic acid and vitamin $B_{12}$.

| System organ class | Frequency | Event** | Pemetrexed/ Cisplatin (N = 839) | | Gemcitabine/ Cisplatin (N = 830) | |
|---|---|---|---|---|---|---|
| | | | All grades toxicity (%) | Grade 3 - 4 toxicity (%) | All grades toxicity (%) | Grade 3 - 4 toxicity (%) |
| Blood and lymphatic system disorders | Very common | Hemoglobin decreased | 33.0* | 5.6* | 45.7* | 9.9* |
| | | Neutrophils/ Granulocytes decreased | 29.0* | 15.1* | 38.4* | 26.7* |
| | | Leukocytes decreased | 17.8 | 4.8* | 20.6 | 7.6* |
| | | Platelets decreased | 10.1* | 4.1* | 26.6* | 12.7* |
| Nervous system disorders | Common | Neuropathy-sensory | 8.5* | 0.0* | 12.4* | 0.6* |
| | | Taste disturbance | 8.1 | 0.0*** | 8.9 | 0.0*** |
| Gastrointestinal disorders | Very common | Nausea | 56.1 | 7.2* | 53.4 | 3.9* |
| | | Vomiting | 39.7 | 6.1 | 35.5 | 6.1 |
| | | Anorexia | 26.6 | 2.4* | 24.2 | 0.7* |
| | | Constipation | 21.0 | 0.8 | 19.5 | 0.4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | Stomatitis/ Pharyngitis | 13.5 | 0.8 | 12.4 | 0.1 |
| | | Diarrhoea without colostomy | 12.4 | 1.3 | 12.8 | 1.6 |
| | Common | Dyspepsia/ Heartburn | 5.2 | 0.1 | 5.9 | 0.0 |
| Skin and Subcutaneous tissue disorders | Very common | Alopecia | 11.9* | 0*** | 21.4* | 0.5*** |
| | Common | Rash/desquamation | 6.6 | 0.1 | 8.0 | 0.5 |
| Renal and urinary disorders | Very common | Creatinine elevation | 10.1* | 0.8 | 6.9* | 0.5 |
| General disorders and administration site conditions | Very common | Fatigue | 42.7 | 6.7 | 44.9 | 4.9 |

*P-values <0.05 comparing pemetrexed/cisplatin to gemcitabine/cisplatin, using Fisher Exact test.
**Refer to National Cancer Institute CTC (v2.0; NCI 1998) for each Grade of Toxicity.
***According to National Cancer Institute CTC (v2.0; NCI 1998), taste disturbance and alopecia should only be reported as Grade 1 or 2.

For the purpose of this table, a cut-off of 5% was used for inclusion of all events where the reported considered a possible relationship to pemetrexed and cisplatin.

Clinically relevant toxicity that was reported in ≥ 1% and ≤ 5% of the patients that were randomly assigned to receive cisplatin and pemetrexed include: AST increase, ALT increase, infection, febrile neutropenia, renal failure, pyrexia, dehydration, conjunctivitis, and creatinine clearance decrease.

Clinically relevant toxicity that was reported in < 1% of the patients that were randomly assigned to receive cisplatin and pemetrexed include: GGT increase, chest pain, arrhythmia, and motor neuropathy.

Clinically relevant toxicities with respect to gender were similar to the overall population in patients receiving pemetrexed plus cisplatin.

The table below provides the frequency and severity of undesirable effects considered possibly related to study drug that have been reported in > 5% of 800 patients randomly assigned to receive single agent pemetrexed and 402 patients randomly assigned to receive placebo in the single-agent pemetrexed maintenance (JMEN: N= 663) and continuation pemetrexed maintenance (PARAMOUNT: N=539) studies. All patients were diagnosed with Stage IIIB or IV NSCLC and had received prior platinum-based chemotherapy. Patients in both study arms were fully supplemented with folic acid and vitamin $B_{12}$.

| **System organ class** | **Frequency*** | **Event**** | **Pemetrexed*** (N =800)** | | **Placebo*** (N =402)** | |
|---|---|---|---|---|---|---|
| | | | **All grades toxicity (%)** | **Grade 3 – 4 toxicity (%)** | **All grades toxicity (%)** | **Grade 3 - 4 toxicity (%)** |
| Blood and | Very common | Hemoglobin decreased | 14.6 | 3.5 | 4.7 | 0.5 |

| | | | | | | |
|---|---|---|---|---|---|---|
| lymphatic system disorders | Common | Leukocytes decreased | 4.9 | 1.6 | 0.7 | 0.2 |
| | | Neutrophils decreased | 6.9 | 3.3 | 0.2 | 0.0 |
| Nervous system disorders | Common | Neuropathy-sensory | 6.1 | 0.5 | 4.5 | 0.2 |
| Gastrointestinal disorders | Very common | Nausea | 15.1 | 0.6 | 4.0 | 0.2 |
| | | Anorexia | 11.9 | 1.1 | 3.2 | 0.0 |
| | Common | Vomiting | 7.4 | 0.1 | 1.5 | 0.0 |
| | | Mucositis/ stomatitis | 6.0 | 0.5 | 1.7 | 0.0 |
| Hepatobiliary disorders | Common | ALT (SGPT) elevation | 6.3 | 0.1 | 2.2 | 0.0 |
| | | AST (SGOT) elevation | 5.4 | 0.0 | 1.7 | 0.0 |
| Skin and subcutaneous tissue disorders | Common | Rash/ desquamation | 7.6 | 0.1 | 3.2 | 0.0 |
| General disorders and administration site disorders | Very common | Fatigue | 20.8 | 4.6 | 10.4 | 0.5 |
| | Common | Pain | 6.6 | 0.6 | 4.2 | 0.0 |

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Event; NCI = National Cancer Institute; SGOT = serum glutamic oxaloacectic aminotransferase; SGPT = serum glutamic pyruvic aminotransferase.
* Definition of frequency terms: Very common - ≥ 10%; Common - > 5% and < 10%. For the purpose of this table, a cutoff of 5% was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed.
** Refer to NCI CTCAE Criteria (Version 3.0; NCI 2003) for each grade of toxicity. The reporting rates shown are according to CTCAE version 3.0.
*** Integrated adverse reactions table combines the results of the JMEN pemetrexed maintenance (N=663) and PARAMOUNT continuation pemetrexed maintenance (N=539) studies.

Clinically relevant CTC toxicity of any grade that was reported in ≥ 1% and ≤ 5% of the patients that were randomly assigned to pemetrexed include: febrile neutropenia, infection, decreased platelets, decreased creatinine clearance, diarrhoea, constipation, edema, alopecia, increased creatinine, pruritis/itching, fever (in the absence of neutropenia), ocular surface disease (including conjunctivitis), increased lacrimation, decreased glomerular filtration, dizziness and motor neuropathy.

Clinically relevant CTC toxicity that was reported in < 1% of the patients that were randomly assigned to pemetrexed include: allergic reaction/hypersensitivity, erythema multiforme, supraventricular arrhythmia and pulmonary embolism.

Safety was assessed for patients who were randomised to receive pemetrexed (N=800). The incidence of adverse reactions was evaluated for patients who received ≤ 6 cycles of pemetrexed maintenance (N=568), and compared to patients who received > 6 cycles of pemetrexed (N=232). Increases in adverse reactions (all grades) were observed with longer exposure. However, no statistically significant differences in any other individual Grade 3/4/5 adverse reactions were seen.

Serious cardiovascular and cerebrovascular events, including myocardial infarction, angina pectoris, cerebrovascular accident and transient ischaemic attack 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.

Rare cases of hepatitis, potentially serious, have been reported during clinical studies with pemetrexed.

Pancytopenia has been uncommonly reported during clinical trials with pemetrexed.

In clinical trials, cases of colitis (including intestinal and rectal bleeding, sometimes fatal, intestinal perforation, intestinal necrosis and typhlitis) have been reported uncommonly in patients treated with pemetrexed.

In clinical trials, cases of interstitial pneumonitis with respiratory insufficiency, sometimes fatal, have been reported uncommonly in patients treated with pemetrexed.

Uncommon cases of oedema have been reported in patients treated with pemetrexed.

Oesophagitis/ radiation oesophagitis has been uncommonly reported during clinical trials with pemetrexed.

Sepsis, sometimes fatal, has been commonly reported during clinical trials with pemetrexed.

During post marketing surveillance, the following adverse reactions have been reported in patients treated with pemetrexed:

Uncommon cases of acute renal failure have been reported with pemetrexed alone or in association with other chemotherapeutic agents (see section 4.4). Nephrogenic diabetes insipidus and renal tubular necrosis have been reported in post marketing setting with an unknown frequency.

Uncommon cases of radiation pneumonitis have been reported in patients treated with radiation either prior, during or subsequent to their pemetrexed therapy (see section 4.4).

Rare cases of radiation recall have been reported in patients who have received radiotherapy previously (see section 4.4).

Uncommon cases of peripheral ischaemia leading sometimes to extremity necrosis have been reported.

Rare cases of bullous conditions have been reported including Stevens-Johnson syndrome and Toxic epidermal necrolysis which in some cases were fatal.

Rarely, haemolytic anaemia has been reported in patients treated with pemetrexed.

Rare cases of anaphylactic shock have been reported.

Erythematous oedema mainly of the lower limbs has been reported with an unknown frequency.

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 chemonaive 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 $B_{12}$ 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:

**Efficacy of ALIMTA plus cisplatin vs. cisplatin**
**In malignant pleural mesothelioma**

| | **Randomized and treated patients** | | **Fully supplemented patients** | |
|---|---|---|---|---|
| **Efficacy parameter** | **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* | 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 | | 0.001 | |
| Overal 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
* p-value refers to comparison between arms.

** 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/m2 was studied as a single-agent in 64 chemonaive patients with malignant pleural mesothelioma. The overall response rate was 14.1 %.

*NSCLC, second-line treatment*
A 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).

**Efficacy of ALIMTA vs docetaxel in NSCLC - ITT population**

| | **ALIMTA** | **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** | (.82 - 1.20) | |
| ▪ **Non-inferiority p-value (HR)** | .226 | |
| **Progression free survival (months)** | (n = 283) | (n = 288) |
| ▪ **Median** | 2.9 | 2.9 |
| ▪ **HR (95% CI)** | 0.97 (.82 – 1.16) | |
| **Time to treatment failure (TTTF – months)** | (n = 283) | (n = 288) |
| ▪ **Median** | 2.3 | 2.1 |
| ▪ **HR (95% CI)** | 0.84 (.71 - .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.

*NSCLC, first-line treatment*

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

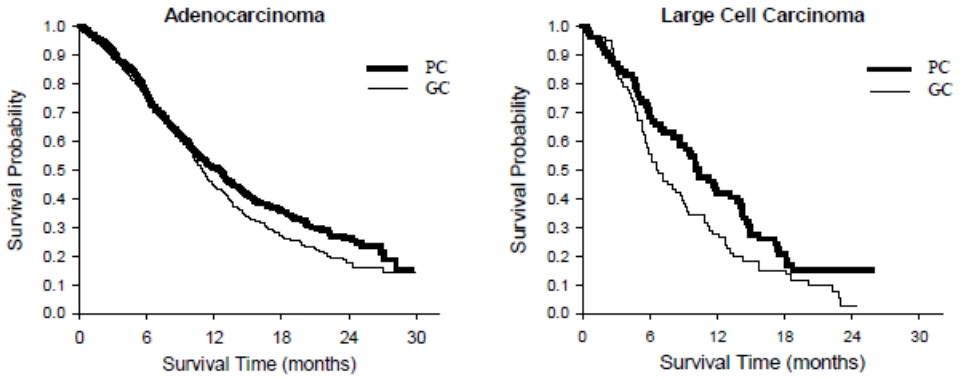
**Efficacy of ALIMTA + cisplatin vs. gemcitabine + cisplatin in first-line non-small cell lung cancer – ITT population and histology subgroups.**

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

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

[a] Statisticaly 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 ≥ 6 cycles and a total of 103 patients (23.4 %) completed ≥ 10 cycles of treatment with pemetrexed.

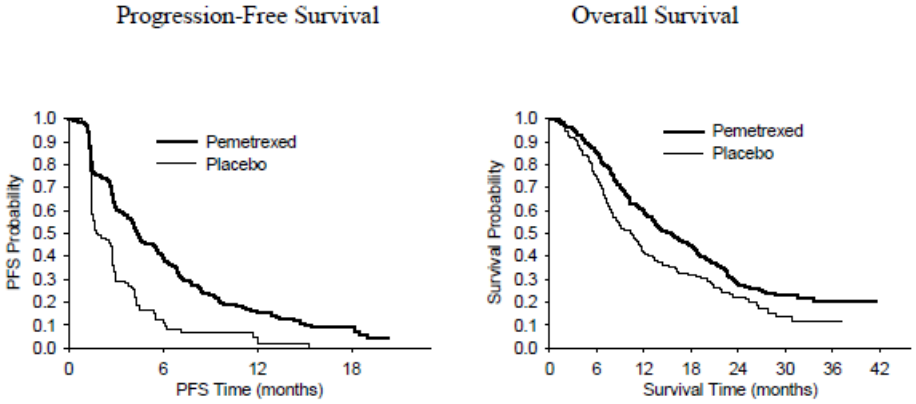
The study met its primary endpoint and showed a statistically significant improvement in PFS in the pemetrexed arm over the placebo arm (n = 581, independently reviewed population; median of 4.0 months and 2.0 months, respectively) (hazard ratio = 0.60, 95% CI = 0.49-0.73, p < 0.00001). The independent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

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

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

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

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



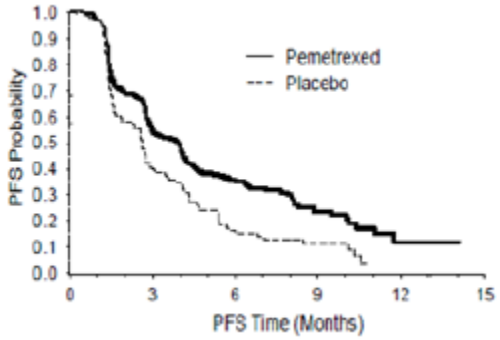

*PARAMOUNT*

A 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).

A preliminary survival analysis showed that the median survival on the ALIMTA continuation arm after induction therapy with ALIMTA/cisplatin (4 cycles) was 13.9 months versus 11.1 months for those on the placebo arm (hazard ration = 0.78, 95% CI = 0.60-0.98, p = 0.034). At the time of this preliminary survival analysis, 48% of patients were alive on the ALIMTA arm versus 38% on the placebo arm, with a median follow-up of 11.04 months.

**PARAMOUNT:Kaplan Meier plot of progression-free survival (PFS) for continuation ALIMTA maintenance versus placebo in patients with NSCLC other than predominantly squamous cell histology (independent review, measured from randomization)**




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$^2$ infused over a 10-minute period. Pemetrexed has a steady-state volume of distribution of 9 L/m$^2$. *In vitro* studies indicate that pemetrexed is approximately 81 % bound to plasma proteins. Binding was not notably affected by varying degrees of renal impairment. Pemetrexed undergoes limited hepatic metabolism. Pemetrexed is primarily eliminated in the urine, with 70 % to 90 % of the administered dose being recovered unchanged in urine within the first 24 hours following administration. 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

Unopened vial

Store below 30ºC.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

### 6.5 Nature and contents of container

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 500 mg; Box of 1 vial. Reg. No.: DKIxxxxxxxxxx

**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

| | | | | | |
|---|---|---|---|---|---|
| X | Proposed truth_v1_ | X | Internal reviewer_YC__ | ☐ | Medical reviewer_____ |
| X | Internal creator_DS_ | ☐ | Approval for Submission | ☐ | Marketing reviewer_____ |
| | | | Date _____ | | |

# Informasi Produk untuk Pasien

## Alimta serbuk injeksi 500mg

## Pemetrexed

Bacalah seluruh leaflet ini dengan seksama sebelum mulai penggunaan obat ini.
- 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

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 ALIMTA
- 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**
ALIMTA tidak relevan digunakan pada populasi anak-anak.

**Pemberian obat-obatan lainnya**
Sampaikan kepada dokter jika sedang mengkonsumsi 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 mengkonsumsi 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.
Selama menggunakan ALIMTA, menyusui harus dihentikan.

**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 500 mg mengandung kurang lebih 54 mg natrium dalam setiap vial. Hal ini untuk dipertimbangkan bagi pasien dengan diet natrium terkontrol.
ALIMTA 100 mg mengandung kurang dari 1 mmol natrium (23 mg) per vial, pada dasarnya "bebas natrium".

## 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 (biasa 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 biasa terjadi). Infeksi (sepsis) dapat menjadi parah dan mengakibatkan kematian.
- Jika mulai terasa sakit di bagian dada (biasa terjadi) atau detak jantung menjadi cepat (tidak biasa terjadi).
- Jika mengalami rasa sakit, kemerahan, pembengkakan atau radang di mulut (sangat biasa terjadi)
- Reaksi alergi: jika terjadi kemerahan di kulit (sangat biasa terjadi)/ rasa terbakar atau tertusuk-tusuk (biasa terjadi), atau demam (biasa 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 biasa 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 sangat biasa terjadi).
- Jika mengalami sesak nafas mendadak, sakit bagian dada yang hebat atau batuk berdahak disertai darah (tidak biasa terjadi) (hal tersebut dapat merupakan pertanda adanya darah beku pada pembuluh darah paru-paru)

Efek samping ALIMTA dapat berupa:

*Sangat biasa terjadi (dapat berpengaruh pada lebih dari 1 dari 10 orang)*
Sel darah putih menjadi rendah
Kadar hemoglobin menjadi rendah (anemia)
Jumlah platetet menjadi rendah
Diare
Muntah
Rasa nyeri, kemerahan, bengkak atau radang di mulut
Mual
Kehilangan nafsu makan
Kelelahan
Kemerahan pada kulit
Kerontokan rambut
Konstipasi (sembelit)
Mati rasa
Ginjal: ketidaknormalan hasil uji darah

*Biasa terjadi (dapat mempengaruhi sampai 1 dari 10 orang)*
Reaksi alergi: kemerahan / rasa terbakar atau tertusuk-tusuk pada kulit
Infeksi termasuk sepsis
Demam
Dehidrasi
Gagal ginjal
Iritasi kulit dan rasa gatal
Nyeri dada
Lemah otot
Konjungtivis (radang pada mata)
Gangguan pada perut
Nyeri di perut
Perubahan indra perasa
Hati: ketidaknormalan hasil uji darah
Mata berair

*Tidak biasa terjadi (dapat mempengaruhi sampai 1 dari 100 orang)*
Gagal ginjal akut
Detak jantung yang cepat
Inflamasi/ radang pada lapisan esofagus (tenggorokan) pernah dialami pada terapi ALIMTA/ radiasi
Colitis (radang pada lapisan usus besar, yang dapat disertai dengan pendarahan usus halus atau rectal)
*Interstitial pneumonitis* (luka pada kantung udara di paru-paru)
Edema (berlebihnya cairan pada jaringan tubuh yang menyebabkan pembengkakan). Beberapa pasien mengalami serangan jantung, stroke atau stroke ringan selama menerima ALIMTA yang biasanya dikombinasikan dengan terapi antikanker lain.
Pansitopenia – kombinasi dari rendahnya jumlah sel darah putih, sel darah merah dan platelet.
Pneumonitis radiasi (luka pada kantung udara di paru-paru yang terkait dengan terapi radiasi) dapat muncul pada pasien yang juga diterapi radiasi baik sebelum, selama atau sesudah dilakukan terapi ALIMTA.
Nyeri pada ektremitas, suhu badan rendah dan perubahan warna pernah dilaporkan
Pembekuan darah di dalam pembuluh darah paru-paru (*pulmonary embolism)*

*Jarang terjadi (dapat mempengaruhi sampai 1 dari 1000 orang)*
*Radiation recall* (kemerahan pada kulit mirip terbakar matahari yang parah) dapat muncul pada kulit yang sebelumnya telah terpapar radioterapi, dalam hitungan hari sampai bertahun-tahun setelah dilakukan radiasi.
*Bullous condition* (penyakit pelepuhan kulit) – termasuk sindrom Stevens-Johnson dan *toxic epidermal necrolysis*
Anemia hemolitik (anemia dikarenakan rusaknya sel darah merah)
Hepatitis (radang pada hati)
Syok anafilaksis (reaksi alergi yang parah).

*Tidak diketahui: Frekuensi tidak bisa diperkirakan dari data yang ada*
Pembengkakan anggota tubuh bagian bawah yang disertai dengan nyeri dan kemerahan
Peningkatan pengeluaran urin
Rasa haus dan peningkatan asupan air
Hypernatremia – peningkatan kadar natrium di darah

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. 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 dan karton.

Obat ini tidak memerlukan kondisi penyimpanan yang khusus.

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 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 isi kemasannya**
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.
Setiap kemasan ALIMTA terdiri atas satu vial.

**Nomor Ijin Edar**
ALIMTA 500 mg: DKI1456600880A1

**HARUS DENGAN RESEP DOKTER**

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