SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

ALIMTA 100 mg powder for solution for infusion

ALIMTA 500 mg powder for solution for infusion

COMPOSITION:

Each vial contains 100 mg or 500 mg pemetrexed as pemetrexed disodium.

Each 100 mg vial must be reconstituted with 4 ml of 0,9% Sodium Chloride injection, without preservative, and each 500 mg vial must be reconstituted with 20 ml of 0,9% Sodium Chloride injection, without preservative. The reconstituted ALIMTA solution contains 25 mg/ml pemetrexed.

Excipients: Mannitol, hydrochloric acid, sodium hydroxide.

PHARMACOLOGICAL CLASSIFICATION:

A 26: Cytostatic agents

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Pemetrexed is a multitarget 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 multitarget antifolate by inhibiting thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyltransferase (GARFT), which are the 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 folyl polyglutamate synthase. 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:

EMPHACIS, a multicentre, randomised, single-blind Phase 3 study of ALIMTA plus cisplatin versus cisplatin in chemonaive patients with malignant 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

	Randomised 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 (95% CI)	12,1 mos (10,0 – 14,4)	9,3 mos (7,8 – 10,7)	13,3 mos (11,4 – 14,9)	10,0 mos (8,4 – 11,9)
Log Rank p-value*	0,020		0,051	
Median Time to tumour progression (95% CI)	5,7 mos (4,9 – 6,5)	3,9 mos (2,8 – 4,4)	6,1 mos (5,3 – 7,0)	3,9 mos (2,8 – 4,5)
Log Rank p-value*	0,001		0,008	
Time to treatment failure (95% CI)	4,5 mos (3,9 – 4,9)	2,7 mos (2,1 – 2,9)	4,7 mos (4,3 – 5,6)	2,7 mos (2,2 – 3,1)
Log Rank p-value*	0,001		0,001	
Overall response rate (95% CI)**	41,3% (34,8 – 48,1)	16,7% (12,0 – 22,2)	45,5% (37,8 – 53,4)	19,6% (13,8 – 26,6)

Efficacy of ALIMTA plus Cisplatin vs Cisplatin in Malignant Pleural Mesothelioma

	Randomised and Treated Patients	Fully Supplemented Patients
Fisher's exact p-value*	<0,001	<0,001

CI = confidence interval

* p-value refers to comparison between arms

** In the ALIMTA/cisplatin arm, randomised and treated (n = 225) and fully supplemented (n = 167)

A statistically significant improvement of the clinically relevant symptoms (pain and dyspnoea) associated with malignant pleural mesothelioma in the ALIMTA/cisplatin arm (212 patients) versus the cisplatin arm alone (218 patients) was demonstrated using the Lung Cancer Symptoms 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 or ALIMTA in combination with carboplatin.

ALIMTA at a dose of 500 mg/m^2 was studied as a single agent in 64 chemonaive patients with malignant pleural mesothelioma. The overall response rate was 14,1%.
ALIMTA at doses ranging from 400 – 600 mg/m^2 was studied in 27 chemonaive malignant pleural mesothelioma patients in combination with carboplatin at doses ranging from AUC 4 - 6, each given once every 21 days. Overall response rate was 32%.

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 clinically meaningful 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).

Efficacy of ALIMTA vs docetaxel in NSCLC – ITT population

	ALIMTA	Docetaxel
Survival time (months)	(n = 283)	(n = 288)
▪ Median	8,3	7,9
▪ 95% CI for median	(7,0 – 9,4)	(6,3 – 9,2)
▪ HR	0,99	
▪ 95% CI for HR	(0,82 – 1,20)	
▪ Non-inferiority p-value (HR)	0,226	
▪ % of docetaxel's survival benefit retained	102%	
▪ 95% CI for % retention	(52 – 157%)	
▪ Non-inferiority p-value (% retention)	0,047	
Progression free survival (months)	(n = 283)	(n = 288)
▪ Median	2,9	2,9
▪ HR (95% CI)	0,97 (0,82 – 1,16)	
Time to Treatment failure (TTTF – months)	(n = 283)	(n = 288)
▪ Median	2,3	2,1
▪ HR (95% CI)	0,84 (0,71 - 0,997)	
Response (n: qualified for response)	(n = 264)	(n = 274)
▪ Response rate (%) (95% CI)	9,1 (5,9 – 13,2)	8,8 (5,7 – 12,8)
▪ Stable disease (%)	45,8	46,4

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

Pharmacokinetic properties:

The pharmacokinetics of pemetrxed 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 16,1 litres. *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 drug being recovered unchanged in the 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.

INDICATIONS:

ALIMTA is indicated for the treatment of patients with malignant pleural mesothelioma in combination with cisplatin. ALIMTA is indicated as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

CONTRA-INDICATIONS:

ALIMTA is contraindicated in patients with known hypersensitivity to pemetrexed or to any of the excipients.

WARNINGS:

ALIMTA can suppress bone marrow function as manifested by neutropenia, thrombocytopenia, anaemia or pancytopenia. (See “Side effects and special precautions”). Myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for myelosuppression during therapy and ALIMTA 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 “Dosage and directions for use”).

In the Phase 3 mesothelioma EMPHACIS trial, less overall 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 patients treated with ALIMTA must be instructed to take folic acid and vitamin B_{12} as a prophylactic measure to reduce treatment-related toxicity. (See “Dosage and directions for use”).

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 "Dosage and directions for use").

An insufficient number of patients has been studied with creatinine clearance of <45 ml/min. Therefore the use of ALIMTA in patients with creatinine clearance of <45 ml/min is not recommended. (See "Dosage and directions for use").

Patients with mild to moderate renal insufficiency (creatinine clearance from 45 – 79 ml/min) should avoid taking non-steroidal anti-inflammatory drugs (NSAIDs) with short-elimination half-lives for at least 2 days prior to, on the day of, and at least 2 days after administration of ALIMTA. All patients eligible for ALIMTA therapy should avoid taking NSAIDs with long elimination half-lives at least 5 days prior to, on the day of, and at least 2 days after ALIMTA administration. (See "Interactions").

The effect of third space fluid, such as pleural effusion or ascites, on ALIMTA is unknown. In patients with clinically significant third space fluid, consideration should be given to draining the effusion prior to ALIMTA administration.

INTERACTIONS:

ALIMTA is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. Concomitant administration of nephrotoxic medicines could result in delayed clearance of ALIMTA. Concomitant administration of substances that are tubularly secreted (e.g. probenecid) could potentially result in delayed clearance of ALIMTA.

Although ibuprofen (400 mg four times daily) can be administered with ALIMTA in patients with normal renal function (creatinine clearance ≥80 ml/min), caution should be used when administering ibuprofen concurrently with ALIMTA to patients with renal insufficiency (creatinine clearance 45 – 79 ml/min). Clinical trials have shown a decrease in ALIMTA clearance following co-administration of ibuprofen. It is recommended that patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives at least 2 days prior to, on the day of, and at least 2 days after administration of ALIMTA.

In the absence of data regarding potential interaction between ALIMTA and NSAIDs with longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least 5 days before, on the day of, and at least 2 days after ALIMTA administration. If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression and gastrointestinal toxicity.

Acetylsalicylic acid, administered in low to moderate doses (325 mg orally every 6 hours) does not affect the pharmacokinetics of ALIMTA.

The pharmacokinetics of ALIMTA are not influenced by concurrently administered cisplatin or carboplatin. Similarly, the pharmacokinetics of total platinum are unaltered by ALIMTA. Oral folic acid and intramuscular vitamin B_{12} supplementation do not affect the pharmacokinetics of ALIMTA.

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

PREGNANCY AND LACTATION:

Pregnancy:

There is no data on the use of ALIMTA in pregnant women. Animal studies have shown reproductive toxicity such as birth defects and other defects on the development of the foetus, the course of gestation and peri- and post-development. The potential risk for humans is unknown. Therefore the use of ALIMTA should be avoided during pregnancy due to the potential hazard to the foetus. Women should also be advised to avoid becoming pregnant while being treated with ALIMTA.

Lactation:

It is not known whether ALIMTA is excreted in human milk. Therefore it is not recommended that breast-feeding be continued during ALIMTA therapy.

DOSAGE AND DIRECTIONS FOR USE:

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

The ALIMTA solution must be prepared as follows:

1. Use appropriate aseptic technique during the reconstitution and further dilution of ALIMTA for intravenous administration.
2. Calculate the dose and number of ALIMTA vials needed. The vial contains an excess of ALIMTA to facilitate delivery of the label amount.
3. Prior to administration, each 500 mg vial must be reconstituted with 20 ml of 0,9% Sodium Chloride Injection, without preservative, resulting in a solution with a concentration of approximately 25 mg/ml ALIMTA. Slowly add the 0,9% Sodium Chloride Injection, without preservative, to the vial and gently swirl until the powder is completely dissolved.
4. **The reconstituted ALIMTA solution must be further diluted with 0,9% Sodium Chloride Injection, without preservative,** prior to intravenous infusion. Further dilute the appropriate volume of the reconstituted ALIMTA solution to 100 ml of 0,9% Sodium Chloride Injection, without preservative. The bag should be inverted gently to mix the solution to obtain a homogeneous solution.
5. ALIMTA contains no antibacterial preservative. For the reconstituted solution, chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 – 8°C, unless reconstitution or dilution has taken place in controlled and validated aseptic conditions.
6. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration.
7. ALIMTA solution should then be administered by intravenous infusion over 10 minutes.
8. Procedures for proper handling and disposal should be observed. As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions of ALIMTA. Any unused contents of the vial should be discarded.

INCOMPATABILITIES:

ALIMTA should ONLY be reconstituted and diluted with 0,9% Sodium Chloride Injection, without preservative. (See preparation instructions above). ALIMTA is compatible with standard polyvinyl chloride administration sets and intravenous solution bags. ALIMTA is physically incompatible with lactated Ringer's Injection and Ringer's Injection.

Co-administration of ALIMTA with other drugs and diluents has not been studied and therefore is not recommended.

Malignant pleural mesothelioma:

Combination use with cisplatin:

Adults: In patients treated for malignant pleural mesothelioma, the recommended dose of ALIMTA is 500 mg/m^2 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 infused over 2 hours approximately 30 minutes after completion of ALIMTA infusion on the first day of each 21-day cycle. Patients should receive hydration consistent with local practice prior to and/or after receiving cisplatin. See cisplatin package insert for specific dosing advice.

Non-small cell lung cancer:

Single agent use:

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

Premedication regimen:

To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after ALIMTA administration. The corticosteroid should be equivalent to 4 mg of dexamethasone administered orally twice a day. (See "Side effects and special precautions").

To reduce toxicity, patients treated with ALIMTA should also receive vitamin supplementation (See "Side effects and special precautions"). Patients must take oral folic acid or multivitamin containing folic acid (350 to 1000 µg)

on a daily basis. At least 5 daily doses of folic acid must be taken during the 7 days preceding the first dose of ALIMTA, and dosing should continue during the full course of therapy and for 21 days after the last dose of ALIMTA. Patients must also receive an intramuscular injection of vitamin B_{12} (1000 µg) in the week preceding the first dose of ALIMTA and every 3 cycles thereafter.

Monitoring:

Patients receiving ALIMTA should be monitored before each dose with a full blood count, including a differential and platelet count. Periodic blood chemistry tests should be collected to evaluate renal and hepatic function. Absolute Neutrophil Count (ANC) should be ≥1500 cells/mm^3 and platelets should be ≥100 000 cells/mm^3 prior to the start of each cycle.

Dose adjustments:

Dose adjustments at the start of a subsequent cycle should be based on nadir haematologic counts or maximum non-haematolgic toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery, patients may 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 A SINGLE AGENT OR IN COMBINATION) AND CISPLATIN: HAEMATOLOGIC TOXICITIES	
Nadir ANC <500/mm^3 and nadir platelets ≥50 000/mm^3	75% of previous dose (both drugs)
Nadir platelets ≤50 000/mm^3 regardless of nadir ANC	50% of previous dose (both drugs)

If patients develop non-haematologic toxicities (excluding neurotoxicity) ≥Grade 3 (with the exception of Grade 3 transaminase elevations), 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 of cisplatin (mg/m^2)**
Any Grade 3[c] or 4 toxicities except mucositis	75% of previous dose	75% of previous dose
Any diarrhoea requiring hospitalisation (irrespective of grade) or Grade 3 or 4 diarrhoea	75% of previous dose	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose	100% of previous dose

[a] National Cancer Institute Common Toxicity Criteria (CTC)

[b] Excluding neurotoxicity

[c] Except Grade 3 transaminase elevation

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 A SINGLE AGENT OR IN COMBINATION) AND CISPLATIN: NEUROTOXICITY		
CTC* Grade	**Dose of ALIMTA (mg/m^2)**	**Dose of Cisplatin (mg/m^2)**
0 – 1	100% of previous dose	100% of previous dose
2	100% of previous dose	50% of previous dose

* Common Toxicity Criteria (CTC)

Treatment with ALIMTA should be discontinued if a patient experiences any haematologic or non-haematologic Grade 3 or 4 toxicity after two dose reductions (except Grade 3 transaminase elevations) 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.

Paediatrics: ALIMTA is not recommended for use in patients under 18 years of age, as safety and efficacy have not been established in this group of patients.

Patients with renal impairment (Standard Cockcroft and Gault formula or Glomerular Filtration Rate measured Tc99m-DPTA serum clearance method): ALIMTA is primarily eliminated unchanged by renal excretion. In clinical studies, patients with creatinine clearance of ≥45 ml/min required no dosage adjustments other than those recommended to all patients. There are insufficient data on the use of ALIMTA in patients with creatinine clearance below 45 ml/min; therefore the use of ALIMTA is not recommended. (See "Side effects and Special Precautions").

Patients with hepatic impairment: No relationships between AST (SGOT), ALT (SGPT), or total bilirubin and ALIMTA pharmacokinetics were identified. However, patients with hepatic impairment such as bilirubin >1,5 times the upper limit of normal and/or transaminase >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.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Effect 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 ALIMTA may cause fatigue. Therefore patients should be cautioned against driving or operating machinery.

Side effects:

Clinical trial data:

The table below provides the frequency and severity of undesirable effects that have been reported in >5% of 429 patients with untreated mesothelioma (n = 43), untreated advanced breast cancer (n = 61), or advanced breast cancer previously treated with at least 3 lines of chemotherapy (n = 60) or advanced non-small cell lung cancer previously treated with one line chemotherapy (n = 265) who received single agent ALIMTA 500 mg/m^2 with folic acid and vitamin B_{12} supplementation.

TABLE 4

System Organ Class	Frequency	Event*	All Grades Toxicity (%)	Grade 3 – 4 Toxicity (%)
Blood and lymphatic system disorders	Very common	Leukocytes decreased	15,2	5,4
		Haemoglobin decreased	14,9	3,3
		Neutrophils/ granulocytes decreased	14,7	8,2
	Common	Platelets decreased	7,0	2,3
Gastro-intestinal disorders	Very common	Nausea	39,2	2,6
		Vomiting	19,6	2,1
		Anorexia	18,6	1,4
		Stomatitis/ pharyngitis	15,4	0,7
		Diarrhoea without colostomy	15,2	0,9
	Common	Constipation	6,1	0,0
General disorders	Very common	Fatigue	34,0	4,7
	Common	Fever	6,8	0,0
Hepato-biliary disorders	Common	ALT (SGPT)	15,6	7,0
		AST (SGOT)	13,1	4,4
Skin and subcutaneous disorders	Very common	Rash/ desquamation	15,9	0,2
	Common	Alopecia	7,0	0,2
		Pruritus	5,8	0,2

System Organ Class	Frequency	Event*	All Grades Toxicity (%)	Grade 3 – 4 Toxicity (%)

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

Very common: ≥10%

Common: >5% and <10%

(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 ALIMTA)

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

Clinically relevant CTC toxicities that were reported in ≤1% of the patients that were randomly assigned to ALIMTA include erythema multiforme and supraventricular tachycardia.

In combination with cisplatin (MPM):

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 ALIMTA, and 163 patients with mesothelioma randomised to receive single agent cisplatin. In both treatment arms, these chemo-naïve patients were fully supplemented with folic acid and vitamin B_{12}.

TABLE 5

System Organ Class	Frequency	Event*	ALIMTA/cisplatin (n = 168)		Cisplatin (n = 163)	
			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

System Organ Class	Frequency	Event*	ALIMTA/cisplatin (n = 168)		Cisplatin (n = 163)	
			All Grades Toxicity (%)	Grade 3 – 4 Toxicity (%)	All Grades Toxicity (%)	Grade 3 – 4 Toxicity (%)
		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
Gastro-intestinal disorders	Very common	Nausea	82,1	11,9	76,7	5,5
		Vomiting	56,5	10,7	49,7	4,3
		Stomatitis/ pharyngitis	23,2	3,0	6,1	0,0
		Anorexia	20,2	1,2	14,1	0,6
		Diarrhoea	16,7	3,6	8,0	0,0
		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	Neuropathy – sensory	10,1	0,0	9,8	0,6
	Common	Dysgeusia	7,7	0,0	6,1	0,0
Renal disorders	Very common	Serum creatinine elevation	10,7	0,6	9,8	1,2

System Organ Class	Frequency	Event*	ALIMTA/cisplatin (n = 168)		Cisplatin (n = 163)	
			All Grades Toxicity (%)	Grade 3 – 4 Toxicity (%)	All Grades Toxicity (%)	Grade 3 – 4 Toxicity (%)
		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 for the term 'creatinine clearance decreased** which is derived from the CTC term "renal/genitourinary - other".

Very common: ≥10%

Common: >5% and <10%

(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 ALIMTA and cisplatin)

Clinically relevant CTC toxicity that was reported in >1% and ≤5% (common) of all the patients that were randomly assigned to receive cisplatin and ALIMTA include increased AST, ALT and GGT, infection, febrile neutropenia, renal failure, chest pain, pyrexia and urticaria.

Clinically relevant CTC toxicity that was reported in ≤1% of the patients that were randomly assigned to receive cisplatin and ALIMTA include arrhythmia and motor neuropathy.

Single agent ALIMTA (NSCLC):

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 ALIMTA 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 metastatic non-small cell lung cancer and received prior chemotherapy.

TABLE 6

System Organ Class	Frequency	Event*	ALIMTA (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	Haemoglobin decreased	19,2	4,2	22,1	4,3
		Leukocytes decreased	12,1	4,2	34,1	27,2
		Neutrophils/ granulocytes decreased	10,9	5,3	45,3	40,2
	Common	Platelets decreased	8,3	1,9	1,1	0,4
Gastro-intestinal disorders	Very common	Nausea	30,9	2,6	16,7	1,8
		Anorexia	21,9	1,9	23,9	2,5
		Vomiting	16,2	1,5	12,0	1,1
		Stomatitis/ pharyngitis	14,7	1,1	17,4	1,1
		Diarrhoea	12,8	0,4	24,3	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
Hepato-biliary disorders	Common	ALT (SGPT)	7,9	1,9	1,4	0,0
		AST (SGOT)	6,8	1,1	0,7	0,0
Skin and subcutaneous	Very common	Rash/ desquamation	14,0	0,0	6,2	0,0

System Organ Class	Frequency	Event*	ALIMTA (n = 265)		Docetaxel (n = 276)	
			All Grades Toxicity (%)	Grade 3 – 4 Toxicity (%)	All Grades Toxicity (%)	Grade 3 – 4 Toxicity (%)
disorders	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.

Very common: ≥10%

Common: >5% and <10%

(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 ALIMTA)

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

Clinically relevant CTC toxicities that were reported in ≤1% of the patients that were randomly assigned to ALIMTA include supraventricular arrhythmias.

Clinically relevant Grade 3 and Grade 4 laboratory toxicities were similar between integrated Phase 2 results from three single agent ALIMTA studies (n = 164) and the Phase 3 single agent ALIMTA study described above, with the exception of neutropenia (12,8% versus 5,3% respectively) and alanine transaminase 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.

Post-Marketing data: *Gastrointestinal:* Rare cases of colitis have been reported in patients treated with Alimta.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Reported symptoms of overdose include neutropenia, anaemia, thrombocytopenia 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 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 leucovorin in the management of ALIMTA overdosage should be considered.

IDENTIFICATION:

100 mg: A white to either light yellow or green-yellow lyophilised solid in a 10 ml Type I clear glass vial, closed with a grey bromobutyl rubber stopper and sealed with an aluminium seal with a polypropylene flip-cap.
500 mg: A white to either light yellow or green-yellow lyophilised solid in a 50 ml Type I clear glass vial, closed with a grey bromobutyl rubber stopper and sealed with an aluminium seal with a polypropylene flip-cap.

PRESENTATION:

Single vial packs

STORAGE INSTRUCTIONS:

Store at room temperature at or below 25 °C. Keep out of reach of children.

REGISTRATION NUMBER:

100 mg: To be allocated

500 mg: 39/26/0028

NAME AND BUSINESS ADDRESS OF HOLDER OF THE CERTIFICATE OF REGISTRATION:

Eli Lilly (SA) (Pty) Ltd

1 Petunia Rd

BRYANSTON 2021

South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT:

02 December 2005 (500 mg strength)

b) Package insert Veterinary Medicine

The under-mentioned information with regard to this medicine shall appear on the package insert. The information shall be presented in the format stipulated, provided that the Council may authorise any deviation from such information or such format (refer to Regulation 40 of the Act).

1 The words "**Veterinary Medicine**"
2 Scheduling status
3 Proprietary name and dosage form
4 Dosage form
5 Composition
6 Pharmacological classification
7 Pharmacological action (Pharmacokinetics and pharmacodynamics)
8 Indications
9 Contra-indications
10 Warnings or withdrawal period in the case of food-producing animals
11 Dosage and directions for use including age and species dosage
12 Side effects and special precautions for use per species
13 Known signs of overdosage and particulars of its treatment per species
14 Conditions of registration
15 Identification
16 Presentation
17 Storage instructions
18 Registration number
19 Name and business address of the holder of the certificate of registration
20 Date of publication of the package insert.

Not applicable.

c) Patient information leaflet

The under-mentioned information with regard to this medicine shall appear on the patient information leaflet. The information shall be presented in the format stipulated, provided that the Council may authorise any deviation from such information or such format (refer to Regulation 10 of the Act).

1 Scheduling status
2 Proprietary name and dosage form
3 Composition of the medicine, that is, what this medicine contains
4 Approved indication and use, that is, what this medicine is used for
5 Instruction before taking the medicine
6 Instructions on how to take the medicine
7 Side effects
8 Storage and disposal information
9 Presentation
10 Identification
11 Registration number
12 Name and business address of the holder of the certificate of registration
13 Date of publication of the Patient Information Leaflet.

See attached hereto.

ALIMTA 100 mg

Powder for solution for infusion

Powder for solution for infusion

Read all of this leaflet carefully before you start receiving Alimta. Keep this leaflet, as you may want to read it again.

If you have further questions, please ask your doctor or pharmacist.

The medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

Scheduling status:

S4 (To be confirmed for 100 mg)

Proprietary name and dosage form:

Alimta 100 mg or 500 mg powder for solution for injection.

Composition of the medicine (what the medicine contains):

Each vial contains 100 mg or 500 mg pemetrexed which will be reconstituted with 4,2 ml or 20 ml respectively of 0,9% Sodium Chloride Injection without preservative. After reconstitution, the solution contains 25 mg/ml of the active substance pemetrexed. The other ingredients are mannitol, hydrochloric acid and sodium hydroxide.

Approved indication and use (what the medicine is used for):

Alimta is a medicinal agent used in the treatment of cancer.

Alimta is a powder for solution in a vial. Each vial contains 100 mg or 500 mg of the active substance pemetrexed. A hospital pharmacist, nurse or doctor will have mixed the Alimta powder with sterile Sodium Chloride solution before it is given to you by infusion into one of your veins.

Alimta is a treatment for malignant pleural mesothelioma, which is given in combination with cisplatin, another anti-cancer medicine. Malignant pleural mesothelioma is a cancer which affects the lining of the chest cavity.

Alimta is also used for the advanced stage of lung cancer (of a certain type called non-small cell type) after other chemotherapy has been used.

Alimta inhibits the growth of the tumour cells and may reduce tumour size.

Instructions before taking the medicine:

Before you are given Alimta, your doctor will give you oral folic acid (a B-vitamin) and an intramuscular injection of vitamin B_{12}. You must continue to take the folic acid during treatment with Alimta and for 21 days after your last treatment with Alimta. This reduces the toxicity of Alimta.

Before you are given Alimta, your doctor will also give you steroid tablets (dexamethasone or a similar medicine). This can reduce the frequency or severity of skin reactions. If you have any questions, ask your doctor.

Follow all your doctor's instructions carefully.

You should not be given Alimta if you are hypersensitive (allergic) to pemetrexed or any of the ingredients of Alimta listed at the beginning of this leaflet. If you think you may be allergic, ask your doctor for advice.

Take special care with Alimta in the following cases:

If you have or have had problems with your kidneys, talk to your doctor or hospital pharmacist, as you may not be able to have Alimta.

If you are pregnant or think you may be, or are breast-feeding, discuss it with your doctor before you receive Alimta.

Before each infusion, you will have samples of your blood taken to check that you have enough blood cells to receive Alimta. Your doctor may decide to change the dose or put off treating you depending on your general condition and if your blood cell counts are too low.

Please tell your doctor if you are taking any medicine for pain or inflammation (swelling) including medicines purchased without a doctor's prescription. Do not take a long-acting anti-inflammatory medicine during the period 5 days before to at least 2 days after receiving Alimta, including the day you receive your treatment. If you are unsure that your anti-inflammatory has a long duration of activity, discuss it with your doctor or hospital pharmacist before receiving Alimta. In addition, if you have problems with your kidneys, tell your doctor or hospital pharmacist, as you may not be able to take short-acting anti-inflammatory medicines during the period at least 2 days before to at least 2 days after receiving Alimta, including the day you receive your treatment.

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

Pregnancy

If you are pregnant, thinking about becoming pregnant, or think you may be, **tell your doctor.** The use of Alimta should be avoided during pregnancy. Your doctor will discuss with you the potential risk of taking Alimta during pregnancy. If your female partner is considering becoming pregnant, tell your doctor.

Breast-feeding:

If you are breast-feeding, tell your doctor. It is recommended that breast-feeding be stopped during Alimta treatment.

Driving and using machines:

Alimta may make you feel tired. Be careful when driving a car or operating machinery.

Taking other medicines:

Please tell your doctor or hospital pharmacist if you are taking or have recently taken any other medicines, even those not prescribed by a doctor.

Instructions on how to take the medicine:

The dose you need is based on your height and weight (which is used to calculate your body surface area). The dosage may be adjusted, or treatment may be delayed depending on your blood cell counts and on your general condition.

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

You should usually receive your infusion once every 3 weeks.

When using Alimta in combination with cisplatin:

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

Additional medicines:

Corticosteroids: it is recommended that you take steroid tablets (equivalent to 4 mg of dexamethasone twice a day) on the day before, on the day of, and on the day after Alimta treatment. This medicine is

given to you to reduce the frequency and severity of skin reactions that you may experience during your anticancer treatment.

Vitamin supplementation: you must take oral folic acid or a multivitamin containing folic acid (350 to 1000 micrograms) once a day while you are taking Alimta. You should take at least 5 doses during the 7 days before the first dose of Alimta. You must continue taking the folic acid for 21 days after the last dose of Alimta. You will also receive an injection of vitamin B_{12} (1000 micrograms) in the week before administration of Alimta and then approximately every 2 to 3 months (corresponding to 3 courses of Alimta treatment). Vitamin B12 and folic acid are given to you to reduce the possible toxic effects of the anticancer treatment.

Side-effects:

Like all medicines, Alimta can have side effects:

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

- Fever or infection: if you have a temperature of 38 °C or greater, sweating or other signs of infection (since you might have less white cells than normal)
- If you start feeling chest pain or having a fast heart rate
- If you have pain, redness, swelling or sores in your mouth
- Allergic reaction: if you develop skin rash, swollen lips, or have trouble catching your breath
- If you experience tiredness, feeling faint, becoming easily breathless or if you look pale (since you might have less haemoglobin than normal)
- If you experience bleeding from the gums, nose or mouth or any bleeding that would not stop, reddish or pinkish urine, unexpected bruising (since you might have less platelets than normal)

Other effects may include:

- General: fatigue (tiredness), dehydration

- Gastroinstestinal tract: pain in the abdomen, upset stomach, constipation, nausea, vomiting, loss of appetite, diarrhoea
- Nervous system: taste change, loss of sensation, muscle weakness
- Skin: irritation of the skin, itching, hair loss, burning or prickling sensation
- Eye disorders: conjunctivitis (inflamed eye)
- Liver and kidney: abnormal blood tests, kidney failure

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

If you are concerned about any side effect(s), talk to your doctor.

If you notice any side effect(s) not mentioned in this leaflet, please inform your doctor or pharmacist.

Storage and disposal information:

Keep out of reach and sight of children. Store at room temperature at or below 25 °C.

Identification:

A white to either light yellow or green-yellow lyophilised solid in a 10 ml (100 mg strength) or 50 ml (500 mg strength) Type I glass vial, closed with a bromobutyl rubber stopper and sealed with an aluminium seal with a polypropylene flip-cap.

Presentation:

Single vial packs

Registration number:

100 mg: 42/26/0448

500 mg: 39/26/0028

Name and address of the holder of the certificate of registration:

Eli Lilly (SA) (Pty) Ltd

1 Petunia St

Bryanston 2021

South Africa

Date of publication of the Patient Information Leaflet:

06 March 2014