NEW ZEALAND DATASHEET

1. PRODUCT NAME

ALIMTA® 100mg powder for infusion

ALIMTA® 500mg powder for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mg vial contains pemetrexed disodium equivalent to 100 mg pemetrexed. Each 100 mg vial must be reconstituted with 4.2 mL of 0.9 % Sodium Chloride Injection (preservative free). The reconstituted ALIMTA solution contains 25 mg/mL of pemetrexed.

The 500 mg vial contains 500 mg of pemetrexed as pemetrexed disodium. Each 500 mg vial must be reconstituted with 20 mL of 0.9 % Sodium Chloride Injection (preservative free). The reconstituted ALIMTA solution contains 25 mg/mL of pemetrexed.

For the full list of excipients, see **6.1 List of excipients**.

3. PHARMACEUTICAL FORM

ALIMTA is supplied as a sterile lyophilised powder for intravenous infusion available in single dose vials. The product is a white to either light yellow or green-yellow lyophilised solid.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Malignant Pleural Mesothelioma

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

Non-small cell lung cancer

ALIMTA in combination with cisplatin is indicated for initial treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.

ALIMTA as monotherapy is indicated for treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology after prior platinum-based chemotherapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

ALIMTA should only be administered under the supervision of a physician qualified in the use of anticancer chemotherapy. The ALIMTA solution must be prepared according to the instructions provided (see **4.2 Dose and method of administration- Instructions for Use and Handling**).

Combination use with cisplatin:
The recommended dose of ALIMTA is 500 mg/m^2 as 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 should receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving cisplatin. See cisplatin Data Sheet for specific dosing advice.

Single agent use:

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 **4.4 Special warnings and precautions for use**).

To reduce toxicity, patients treated with ALIMTA should also receive vitamin supplementation (see **4.4 Special warnings and precautions for use**). 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 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 B12 (1000 micrograms) in the week preceding the first dose of ALIMTA and every three cycles thereafter. Subsequent vitamin B12 injections may be given on the same day as ALIMTA.

Monitoring

Patients receiving ALIMTA should be monitored before each dose with a complete 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 greater than or equal to 1500 cells/mm^3 and platelets should be greater than or equal to 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 nonhaematologic 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 – Haematologic Toxicities

Nadir ANC < 500 /mm^3 and nadir platelets greater than or equal to 50,000 /mm^3	75 % of previous dose (ALIMTA and cisplatin)
Nadir platelets 50,000 /mm^3 without bleeding regardless of nadir ANC	75 % of previous dose (ALIMTA and cisplatin)
Nadir platelets <50,000/mm^3 with bleeding[a], regardless of nadir ANC.	50% of previous dose (ALIMTA and cisplatin).

[a] These criteria meet the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 2.0 (NCI 1998) definition of ≥CTC Grade 2 bleeding

If patients develop nonhaematologic toxicities (excluding neurotoxicity) greater than or equal to Grade 3, treatment should be withheld until resolution to less than or equal to the patient's pretherapy 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 – Nonhaematologic Toxicities[a, b]

	Dose of ALIMTA (mg/m^2)	**Dose of cisplatin (mg/m^2)**
Any Grade 3 or 4 toxicities except mucositis	75% of previous dose	75% of previous dose
Any diarrhoea requiring hospitalisation (irrespective of grade) or grade 3 or 4 diarrhoea	75% of previous dose	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose	100% of previous dose

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

[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 Grade	Dose for 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

Treatment with ALIMTA should be discontinued if a patient experiences any haematologic or nonhaematologic Grade 3 or 4 toxicity after 2 dose reductions 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): Pemetrexed is primarily eliminated unchanged by renal excretion. In clinical studies, patients with creatinine clearance of greater than or equal to 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 ALIMTA is not recommended (see 4**.4 Special warnings and precautions for use**).

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.

Instructions for Use and Handling

1. Use appropriate aseptic technique during the reconstitution and further dilution of pemetrexed for intravenous infusion administration.
2. Calculate the dose and number of ALIMTA vials needed. The vial contains an excess of pemetrexed to facilitate delivery of the label amount.
3. Prior to administration, a 500 mg vial must be reconstituted with 20 mL of 0.9% Sodium Chloride Injection (preservative free), resulting in a solution with a concentration of approximately 25 mg/mL pemetrexed. A 100 mg vial must be reconstituted with 4.2 mL of 0.9% Sodium Chloride Injection (preservative free) resulting in a solution with a concentration of 25 mg/mL pemetrexed. Slowly add the 0.9 % Sodium Chloride Injection (preservative free) 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 (preservative free)** prior to intravenous infusion. Further dilute the appropriate volume of the reconstituted ALIMTA solution to 100 mL with 0.9 % Sodium Chloride Injection (preservative free). 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 when refrigerated between 2 to 8°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 to 8°C, unless reconstitution / 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 given 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 pemetrexed. Any unused contents of the vial should be discarded in an appropriate manner.

4.3 CONTRAINDICATIONS

ALIMTA is contraindicated in women of childbearing age unless adequate contraception is used. ALIMTA is contraindicated in patients with known hypersensitivity to pemetrexed or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Pemetrexed can suppress bone marrow function as manifested by anaemia, neutropenia, thrombocytopenia or pancytopenia. (see **4.8 Undesirable effects**). 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 greater than or equal to 1500 cells/mm3 and platelet count returns to greater than or equal to 100,000 cells/mm3. Dose reductions for subsequent cycles are based on nadir ANC, platelet count and maximum nonhaematologic toxicity seen from the previous cycle (see **4.2 Dose and method of administration**).

In the Phase 3 mesothelioma EMPHACIS trial, overall less toxicity and reduction in Grade 3/4 haematologic and nonhaematologic toxicities such as neutropenia, febrile neutropenia and infection with Grade 3/4 neutropenia were reported when pretreatment with folic acid and vitamin B12 was administered. Therefore patients treated with ALIMTA must be instructed to take folic acid and vitamin B12 as a prophylactic measure to reduce treatment-related toxicity (see **4.2 Dose and method of administration**).

Skin reactions have been reported in patients not pretreated with a corticosteroid. Pretreatment with dexamethasone (or equivalent) can reduce the incidence and severity of skin reactions (see **4.2 Dose and method of administration**).

Insufficient numbers of patients have been studied with creatinine clearance of below 45 mL/min. Therefore, the use of ALIMTA in patients with creatinine clearance of < 45 mL/min is not recommended (see **4.2 Dose and method of administration**).

Patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min) should avoid taking nonsteroidal 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 pemetrexed. 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 pemetrexed administration (see **4.5 Interactions with other medicines and other forms of interactions**).

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 tumor 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Nephrotoxic drugs

Pemetrexed is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. In Vitro studies indicate that pemetrexed is actively secreted by OAT3 (organic anion transporter 3). Concomitant administration of nephrotoxic drugs could result in delayed clearance of pemetrexed. Concomitant administration of substances that are also tubularly secreted (e.g. probenecid) could potentially result in delayed clearance of pemetrexed.

NSAIDs

Although NSAIDs in moderate doses can be administered can be administered with pemetrexed in patients with normal renal function (creatinine clearance greater than or equal to 80 mL/min), caution should be used when administering NSAIDs concurrently with pemetrexed to patients with renal insufficiency (creatinine clearance 45 - 79 mL/min). Clinical trials have shown a decrease in pemetrexed clearance following coadministration 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 pemetrexed.

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

Aspirin

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

Concomitant cytotoxic therapy

The pharmacokinetics of pemetrexed are not influenced by concurrently administered cisplatin or carboplatin. Similarly, the pharmacokinetics of total platinum are unaltered by pemetrexed. Oral folic acid and intramuscular vitamin B12 supplementation do not affect the pharmacokinetics of pemetrexed.

Cytochrome P450

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Administration of pemetrexed to male mice resulted in reproductive toxicity characterised by slightly reduced fertility rates and testicular atrophy. This suggests that pemetrexed may impair male fertility.

Use in pregnancy

ALIMTA is contraindicated in women of childbearing age unless adequate contraception is used. There are no data from the use of pemetrexed in pregnant women. Animal studies have shown reproductive toxicity such as birth defects and other effects on the development of the foetus, the course of gestation or peri- and postnatal development (see **4.6 Fertility, pregnancy and lactation and 5.3 Preclinical safety data**). The potential risk for humans

is unknown. Therefore the use of pemetrexed must be avoided during pregnancy due to the potential hazard to the foetus. Women must be advised to avoid becoming pregnant while being treated with ALIMTA.

Use in lactation

It is not known whether pemetrexed is excreted in human milk. Therefore, it is recommended that breastfeeding be discontinued during ALIMTA therapy.

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 ALIMTA may cause fatigue. Therefore patients should be cautioned against driving or operating machinery if this event occurs.

4.8 UNDESIRABLE EFFECTS

Single agent ALIMTA (non-small cell lung cancer)

Table 4 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 B12 supplementation and 276 patients randomly assigned to receive single agent docetaxel. All patients were diagnosed with locally advanced or metastatic NSCLC and received prior chemotherapy.

Table 4						
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	19.2	4.2	22.1	4.3
		Leukocytes	12.1	4.2	34.1	27.2
		Neutrophils/ Granulocyte	10.9	5.3	45.3	40.2
	Common	Platelets	8.3	1.9	1.1	0.4
Gastrointestinal 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
Hepatobiliary 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 Tissue Disorders	Very Common	Rash/ desquamation	14.0	0.0	6.2	0.0
	Common	Pruritis	6.8	0.4	1.8	0.0
		Alopecia	6.4	0.4**	37.7	2.2**

Refer to NCI CTC for lab values for each Grade of toxicity (version 2.0).
** According to NCI CTC (version 2.0), alopecia should only be reported as Grade 1 or 2.

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 toxicity that was 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 toxicity that was reported in <1% (uncommon) 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 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 chemonaive and heavily pre-treated breast cancer patients with pre-existing liver metastases and/or abnormal baseline liver function tests.

Combination with cisplatin (malignant pleural mesothelioma)

Table 5 provides the frequency and severity of adverse 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 B12.

Table 5						
System Organ Class	**Frequency**	**Event***	**Pemetrexed/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	56.0	23.2	13.5	3.1
		Leukocytes	53.0	14.9	16.6	0.6
		Haemoglobin	26.2	4.2	10.4	0.0
		Platelets	23.2	5.4	8.6	0.0
Eye Disorders	Common	Conjunctivitis	5.4	0.0	0.6	0.0
Gastrointestinal 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	Taste disturbance	7.7	0.0***	6.1	0.0***
Renal Disorders	Very Common	Creatinine Clearance Decreased**	10.7	0.6	9.8	1.2
		Renal/ Genitourinary	16.7	0.6	18.4	2.5
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 NCI CTC version 2 for each Grade of toxicity except the term "creatinine clearance decreased"
** which is derived from the CTC term "renal/genitourinary-other".
*** According to NCI CTC (version 2.0), taste disturbance and alopecia should only be reported as Grade 1 or 2.

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 pemetrexed and cisplatin).

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

Clinically relevant 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 considered possibly related to study drug that have been reported in >5% of 839 patients with NSCLC who were randomised to study and received cisplatin and pemetrexed and 830 patients with NSCLC who were randomised to study and received 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 B12.

Table 6

System Organ Class	Frequency	Event*	ALIMTA/cisplatin (N=839)		Cisplatin (N=830)	
			All Grades Toxicity (%)	Grade 3 - 4 Toxicity (%)	All Grades Toxicity (%)	Grade 3 - 4 Toxicity (%)
Blood and Lymphatic System Disorders	Very Common	Haemoglobin	33.0	5.6	45.7	9.9
		Neutrophils/ granulocytes	29.0	15.1	38.4	26.7
		Leukocytes	17.8	4.8	20.6	7.6
		Platelets	10.1	4.1	26.6	12.7
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
General Disorders and Administration site conditions	Very Common	Fatigue	42.7	6.7	44.9	4.9
Nervous System Disorders	Common	Neuropathy-Sensory	8.5	0.0	12.4	0.6
		Taste disturbance	8.1	0.0**	8.9	0.0**
Renal Disorders	Very Common	Creatinine	10.1	0.8	6.9	0.5
Skin and Subcutaneous Tissue disorder	Very Common	Alopecia	11.9	0**	21.4	0.5**
	Common	Rash/ desquamation	6.6	0.1	8.0	0.5

*Refer to NCI CTC (version 2) for each Grade of toxicity.

**According to NCI CTC (version 2), taste disturbance and alopecia should only be reported as Grade 1 or 2

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 pemetrexed and cisplatin).

Clinically relevant toxicity that was reported in ≥1% and ≤5% (common) 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% (uncommon) of the patients that were randomly assigned to receive cisplatin and pemetrexed include: GGT increase, chest pain, arrhythmia, and motor neuropathy.

Single agent ALIMTA (NSCLC maintenance)

Table 7 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 maintenance pemetrexed study (Study JMEN: N=663) and continuation pemetrexed maintenance study (PARAMOUNT: N=539). 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 B12.

Table 7

System Organ Class	Frequency[a]	Event[b]	Pemetrexed (N = 800)		Placebo (N = 402)	
			All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Blood and Lymphatic System Disorders	Very Common	Hemoglobin decreased	18.0	4.5	5.2	0.5
	Common	Leukocytes decreased	5.8	1.9	0.7	0.2
		Neutrophils decreased	8.4	4.4	0.2	0.0
Gastrointestinal Disorders	Very Common	Nausea	17.3	0.8	4.0	0.2
		Anorexia	12.8	1.1	3.2	0.0
	Common	Vomiting	8.4	0.3	1.5	0.0
		Mucositis/ stomatitis	6.8	0.8	1.7	0.0
General Disorders and Administration Site Disorders	Very Common	Fatigue	24.1	5.3	10.9	0.7
	Common	Pain	7.6	0.9	4.5	0.0
		Edema	5.6	0.0	1.5	0.0

Table 7						
System Organ Class	**Frequency[a]**	**Event[b]**	**Pemetrexed (N = 800)**		**Placebo (N = 402)**	
			All Grades (%)	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Hepatobiliary Disorders	Common	ALT (SGPT) elevation	6.5	0.1	2.2	0.0
		AST (SGOT) elevation	5.9	0.0	1.7	0.0
Skin and Subcutaneous Tissue Disorders	Very Common	Rash/ desquamation	8.1	0.1	3.7	0.0
Nervous System Disorders	Common	Neuropathy-sensory	7.4	0.6	5.0	0.2
Renal Disorders	Common	Renal disorders[c]	7.6	0.9	1.7	0.0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Event; NCI = National Cancer Institute; SGOT = serum glutamic oxaloacectic transaminase; SGPT = serum glutamic pyruvic transaminase.

a 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.

b Refer to NCI CTCAE Criteria (Version 3.0; NCI 2003) for each grade of toxicity

c Combined term includes increased serum/blood creatinine, decreased glomerular filtration rate, renal failure and renal/genitourinary – other.

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

Clinically relevant CTC toxicity that was reported in <1% (uncommon) of the patients that were randomly assigned to pemetrexed include: febrile neutropenia, allergic reaction/hypersensitivity, motor neuropathy, erythema multiforme, renal failure, and supraventricular arrhythmia.

The incidence of adverse reactions was evaluated for patients who received ≤ 6 cycles of pemetrexed, and compared to patients who received > 6 cycles of pemetrexed. Increases in adverse reactions (all grades) were observed with longer exposure; however, no statistically significant differences in Grade 3/4 adverse reactions were seen.

In clinical trials, sepsis which in some cases was fatal occurred in approximately 1% of patients.

Cases of oesophagitis have been reported uncommonly in clinical trials with pemetrexed.

POST-MARKETING DATA:

Gastrointestinal Disorders - Rare cases of colitis have been reported in patients treated with ALIMTA.

General disorders and administration site conditions – Rare cases of oedema have been reported in patients treated with ALIMTA.

Injury, poisoning and procedural complications - Rare cases of radiation recall have been reported in patients who have previously received radiotherapy.

Respiratory – Rare cases of interstitial pneumonitis have been reported in patients treated with ALIMTA.

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

Blood and lymphatic system — Rare cases of immune-mediated haemolytic anaemia have been reported in patients treated with pemetrexed.

Rare - ≤0.1% of patients treated with ALIMTA

Reporting of suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 OVERDOSE

Reported symptoms of overdose include neutropenia, anaemia, thrombocytopenia, mucositis, 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 pemetrexed overdose should be considered.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group:, Folic acid analogues, ATC code: L01BA04

ALIMTA (pemetrexed) is a multitarget anticancer 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 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. Data indicates that over expression of thymidylate synthase (TS) correlates with reduced sensitivity to pemetrexed in antifolate-resistant cell lines. Results in a recent study with specimens from chemonaive patients with Non-Small Cell Lung Cancer (NSCLC) demonstrated lower levels of TS expression in adenocarcinoma as compared to squamous cell carcinoma tumors. This data suggests that pemetrexed may offer greater efficacy for patients with adenocarcinoma as compared to squamous carcinoma histology.

Clinical Efficacy

Malignant Pleural Mesothelioma - EMPHACIS, a multicentre, randomised, single-blind Phase 3 study of ALIMTA plus cisplatin versus cisplatin alone 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 B12 supplementation were 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 B12 supplementation during the entire course of study therapy (fully supplemented). The results of these analyses of efficacy are summarised in Table 8.

Table 8 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 months (10.0-14.4)	9.3 months (7.8-10.7)	13.3 months (11.4-14.9)	10.0 months (8.4-11.9)
Log Rank p-value*	0.020		0.051	
Median Time to Tumour Progression (95 % CI)	5.7 months (4.9-6.5)	3.9 months (2.8-4.4)	6.1 months (5.3-7.0)	3.9 months (2.8-4.5)
Log Rank p-value*	0.001		0.008	
Time to Treatment Failure (95 % CI)	4.5 months (3.9-4.9)	2.7 months (2.1-2.9)	4.7 months (4.3-5.6)	2.7 months (2.2-3.1)
Log Rank p-value*	0.001		0.001	
Overall Response Rate** (95 % CI)	41.3 % (34.8-48.1)	16.7 % (12.0-22.2)	45.5 % (37.8-53.4)	19.6% (13.8-26.6)
Fisher's exact p-value*	< 0.001		< 0.001	

Abbreviation: CI = confidence interval.
* 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 alone arm (218 patients) was demonstrated using the Lung Cancer Symptom Scale. Statistically significant differences in pulmonary function tests were also observed. The separation between the treatment arms was achieved by improvement in lung function in the ALIMTA /cisplatin arm and deterioration of lung function over time in the control arm.

There are limited data in patients with malignant pleural mesothelioma treated with ALIMTA alone.

ALIMTA at a dose of 500 mg/m^2 was studied as a single agent in 64 chemonaive patients with malignant pleural mesothelioma. The overall response rate was 14.1%.

Non-Small Cell Lung Cancer — The safety and efficacy of ALIMTA have been evaluated in combination with cisplatin as initial treatment for Non-Small Cell Lung Cancer (NSCLC) and as a single-agent in patients who have previously received chemotherapy 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) 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). Refer to figure below.

Kaplan-Meier Curves for Overall Survival - ALIMTA + Cisplatin (AC) vs. Gemcitabine + Cisplatin in First-line Non-Small Cell Lung Cancer – ITT Population

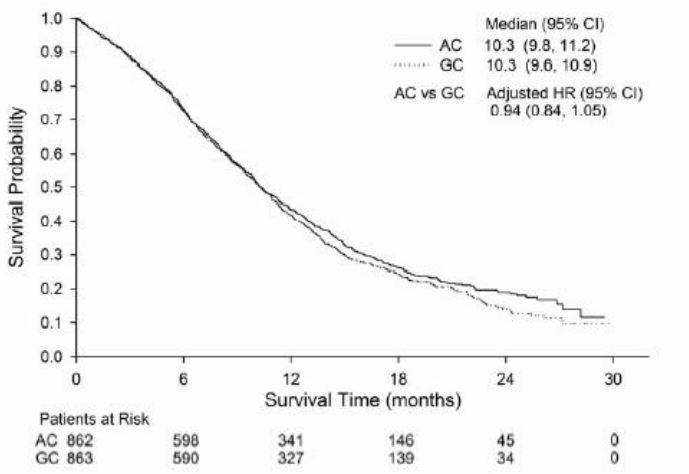


Table 9 Efficacy of ALIMTA + Cisplatin vs. Gemcitabine + Cisplatin in First-line Non-Small Cell Lung Cancer – ITT Population

	ALIMTA + Cisplatin (N= 862)	**Gemcitabine + Cisplatin (N= 863)**
Median overall survival (95% CI)	10.3 mos (9.8 – 11.2)	10.3 mos (9.6 – 10.9)
Adjusted hazard ratio (HR) (95% CI)	0.94[a] (0.84 – 1.05)	
12 month survival probability (95% CI)	43.5% (40.1 – 46.9)	41.9% (38.5 – 45.5)
24 month survival probability (95% CI)	18.9% (15.7 – 22.2)	14.0% (10.9 – 17.1)
Median Progression free survival (95% CI)	4.8 mos (4.6 – 5.3)	5.1 mos (4.6 – 5.5)
Adjusted hazard ratio (HR) (95% CI)	1.04[a] (0.94 – 1.15)	
Overall Response rate [b] (95% CI)	30.6% (27.3% - 33.9%)	28.2% (25.0% - 31.4%)

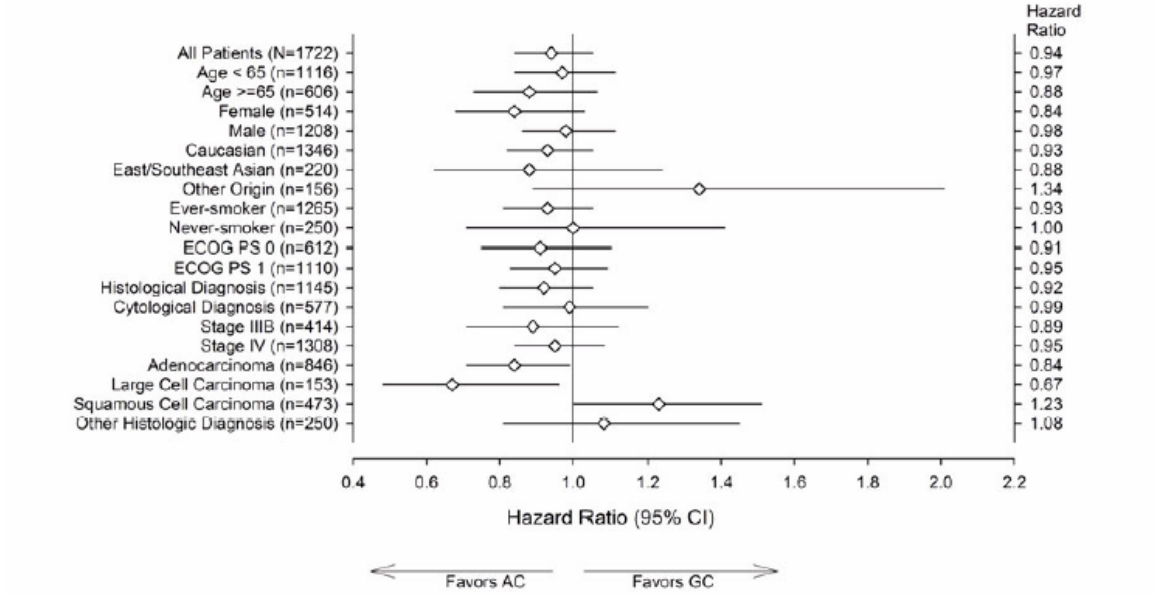
Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent to treat; N = total population size, mos = months.

[a] Statistically significant for non-inferiority

[b] Number of tumor-qualified patients on the AC arm (N=762) and GC arm (N=755). Investigator assessed

A series of subsets of patients were examined in pre-specified adjusted analyses. The results of these analyses are shown in the figure below.

Forest Plot for Overall Survival Adjusted Hazard Ratios of Subgroups ALIMTA + Cisplatin vs. Gemcitabine + Cisplatin in First-line Non-Small Cell Lung Cancer – ITT Population



Results based on Cox adjusted analyses for ECOG PS, disease stage, gender, and basis for diagnosis (histological vs cytological). In the analysis by group, pertaining to each of these 4 covariates, the variable depicting the group was excluded from the model.
3 patients were missing ECOG performance status and are excluded from the Cox adjusted analyses; 209 patients were missing smoking status

Abbreviations: AC = pemetrexed plus cisplatin; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; GC = gemcitabine plus cisplatin.

The analysis of the impact of NSCLC histology on overall survival demonstrated statistically significant superiority for ALIMTA + cisplatin in the adenocarcinoma (n=846, 12.6 versus 10.9 months, adjusted HR = 0.84; 95% CI =0 .71-0.99, p =0.033) and large cell carcinoma subgroups (n=153, 10.4 versus 6.7, adjusted HR =0 .67; 95% CI = 0.48-0.96, p =0.027) but not in patients with squamous cell carcinoma (n=473, 9.4 versus 10.8 months, adjusted HR = 1.23; 95% CI =1.00-1. 51, p =0.050) or patients with other histologies (n=250, 8.6 versus 9.2, adjusted HR = 1.08; 95% CI =0.81-1.45, p =0.586).

In another pre-specified analysis of randomised and treated patients (n=1669), patients treated with ALIMTA + cisplatin showed a statistically significantly longer survival without possibly drug-related grade 4 toxicity compared with gemcitabine + cisplatin (adjusted HR = 0.83; 95% CI = 0.74-0.93, p <0.001); with a median time of 9.8 versus 8.6 months.

Patients treated with ALIMTA and cisplatin required fewer transfusions (16.4% versus 28.9%, p<0.001), red blood cell transfusions (16.1% versus 27.3%, p<.001) and platelet transfusions (1.8% versus 4.5%, p=0.002). Patients treated with ALIMTA and cisplatin also required lower administration of erythropoietin/darbopoietin (10.4% versus 18.1%, p<.001), G-CSF/GM-CSF (3.1% versus 6.1%, p=0.004), and iron preparations (4.3% versus 7.0%, p=0.021).

A multicentre, randomised, double-blind, placebo-controlled Phase 3 study (JMEN), compared the efficacy and safety of maintenance treatment with ALIMTA 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. 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 ALIMTA 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 ALIMTA.

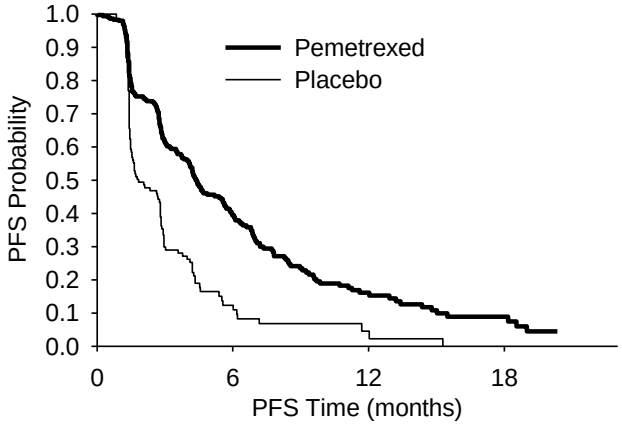
In the overall study population, ALIMTA was statistically superior to placebo in terms of overall survival (OS) (median 13.4 months versus 10.6 months, HR=0.79 (95% CI: 0.65-0.95), p-value=0.012) and PFS (median 4.0 months versus 2.0 months, HR=0.60 (95% CI: 0.49-0.73), p-value<0.00001). Consistent with previous Alimta studies, a difference in treatment outcomes was observed according to histologic classification. For the indicated population i.e. patients with NSCLC other than predominantly squamous cell histology, ALIMTA was superior to placebo for OS (median 15.5 months versus 10.3 months, HR=0.70 (95% CI: 0.56-0.88)) and PFS (median 4.4 months versus 1.8 months, HR=0.47 (95% CI: 0.37-0.60)).

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

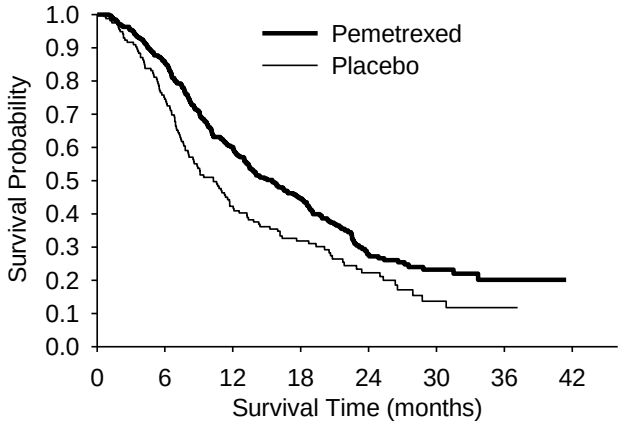
There were no clinically relevant differences observed for the safety profile of ALIMTA within the histology subgroups.

Kaplan Meier Plots of Progression-Free Survival (PFS) and Overall Survival ALIMTA versus Placebo in Patients with NSCLC other than Predominantly Squamous Cell Histology:

Progression-free Survival



Overall Survival



A multicentre, randomised, double-blind, placebo-controlled Phase 3 study (PARAMOUNT), compared the efficacy and safety of continuation maintenance treatment with ALIMTA 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

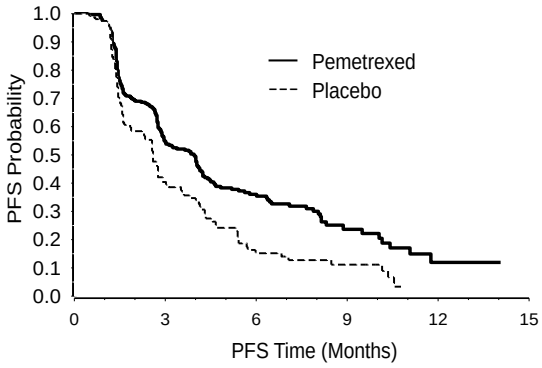
progress after 4 cycles of first line doublet therapy of ALIMTA in combination with cisplatin. Of the 939 patients treated with ALIMTA plus cisplatin induction, 539 patients were randomised to maintenance treatment with ALIMTA or placebo. Of the randomised patients, 44.9% had a complete/partial response and 51.9% had a response of stable disease to ALIMTA plus cisplatin induction. Patients randomised to treatment were required to have an ECOG performance status 0 or 1. The median time from the start of ALIMTA plus cisplatin induction therapy to the start of maintenance treatment was 2.96 months on both the ALIMTA arm and the placebo arm. Randomised patients received maintenance treatment until disease progression. For statistical purposes, 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 ALIMTA and 4 cycles of placebo. A total of 169 patients (47.1%) completed ≥ 6 cycles maintenance treatment with ALIMTA, representing at least 10 total cycles of ALIMTA.

Independent review of the imaging of 472 of the 539 randomised patients showed that the study met its primary endpoint (PFS) and showed a statistically significant improvement in PFS in the ALIMTA arm over the placebo arm – median of 3.9 months and 2.6 months respectively (hazard ration = 0.64, 95% CI = 0.51-0.81, p = 0.0002). The independent review of patient scans showed consistent results to the findings of the investigator assessment of PFS. In addition, for randomised patients, as measured from the start of ALIMTA plus cisplatin first line induction treatment, the median investigator-assessed PFS was 6.9 months for the ALIMTA arm and 5.6 months for the placebo arm (hazard ratio = 0.59, 95% CI = 0.47-0.74).

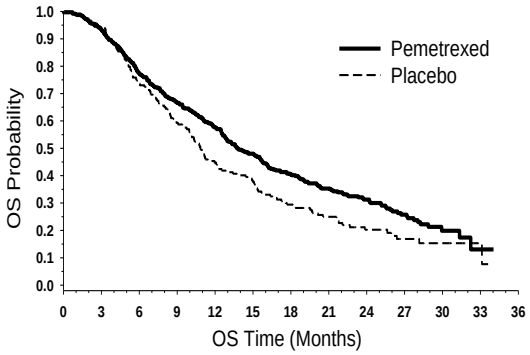
Following ALIMTA plus cisplatin induction (4 cycles), treatment with ALIMTA was statistically superior to placebo for OS (median 13.9 months versus 11.0 months, hazard ratio = 0.78, 95% CI = 0.64-0.96, p = 0.0195). At the time of final survival analysis, 28.7% of patients were alive or lost to follow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

Kaplan Meier Plots of Progression- Free Survival (PFS) and Overall Survival (OS) for Continuation ALIMTA Maintenance versus Placebo in Patients with NSCLC other than Predominantly Squamous Cell Histology (measured from randomization):

Progression-Free Survival



Overall Survival



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

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) which is not statistically significantly different. These data, as outlined in Table 10, indicate comparable efficacy between pemetrexed and docetaxel.

Table 10 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)
▪ Hazard Ratio	0.99	
▪ 95 % CI for Hazard Ratio	(0.82 - 1.20)	
▪ Non-inferiority p-value (Hazard Ratio)	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
▪ Hazard Ratio (95 % CI)	0.97 (.82 - 1.16)	
Time to treatment failure (TTTF – months)	(n = 283)	(n = 288)
▪ Median	2.3	2.1
▪ Hazard Ratio (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; ITT = intent to treat; n = total population size.
* Based on Rothmann analysis.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics 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 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 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.

5.3 PRECLINICAL SAFETY DATA

Administration of pemetrexed to pregnant mice resulted in decreased foetal weight, incomplete ossification of some skeletal structures and cleft palate. The use of pemetrexed must therefore be avoided in pregnant women (see **4.3 Contraindications; 4.6 Fertility, pregnancy and lactation**).

Genotoxicity

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.

Carcinogenicity

Studies to assess the carcinogenic potential of pemetrexed have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol, hydrochloric acid, sodium hydroxide.

6.2 INCOMPATIBILITIES

ALIMTA should ONLY be reconstituted and diluted with 0.9 % Sodium Chloride Injection (preservative free) (see **4.2. Dose and method of administration - Instructions for Use and Handling**). ALIMTA is compatible with standard polyvinyl chloride administration sets and intravenous solution bags. Pemetrexed is physically incompatible with lactated Ringer's Injection and Ringer's Injection.

Co-administration of pemetrexed with other medicines and diluents has not been studied, and therefore is not recommended.

6.3 SHELF-LIFE

Unopened vial

3 years.

Reconstituted Solution

ALIMTA contains no antibacterial preservative. For the reconstituted solution, chemical and physical in-use stability has been demonstrated for 24 hours when refrigerated between 2 to 8°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 to 8°C, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.
Parenteral medicines should be inspected visually for particulate matter and discolouration

prior to administration, whenever solution or container permits.
Any unused contents of the vial should be discarded in an appropriate manner.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Store in the original packaging.

6.5 NATURE AND CONTENTS OF CONTAINER

Lyophilised powder in vial (Type I glass). Each carton contains one 100 mg vial of ALIMTA or one 500 mg vial of ALIMTA.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

ALIMTA is an anticancer medicine. Appropriate handling and disposal procedures should be used.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Eli Lilly and Company (NZ) Limited
Level 1, 123 Ormiston Road
Botany South, Auckland
New Zealand
Contact telephone number: 0800 500 056

9. DATE OF FIRST APPROVAL

29 July 2004

10. DATE OF REVISION

6 June 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformatted data sheet to SPC format and editorial changes.

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