AUSTRALIAN PRODUCT INFORMATION – ALIMTA® (PEMETREXED DISODIUM HEPTAHYDRATE) POWDER FOR SOLUTION FOR INFUSION

1. NAME OF THE MEDICINE

pemetrexed disodium heptahydrate.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ALIMTA is supplied in 500 mg and 100 mg vials.

Each 500 mg vial of ALIMTA contains pemetrexed disodium heptahydrate equivalent to 500 mg pemetrexed. Each 100 mg vial of ALIMTA contains pemetrexed disodium heptahydrate equivalent to 100 mg pemetrexed.

For the full list of excipients, see section **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, in combination with cisplatin, is indicated for the treatment of patients with malignant pleural mesothelioma.

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 the 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 be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents.

ALIMTA in combination use with cisplatin:

Adults - The recommended dose of ALIMTA is 500 mg/m2 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/m2 BSA infused over 2 hours approximately 30 minutes after completion of the ALIMTA infusion on the first day of each 21 day cycle. Patients must receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving cisplatin. See cisplatin Product Information document for specific dosing advice.

Single agent use:

Adults - The recommended dose of ALIMTA is 500 mg/m2 BSA administered as an intravenous infusion over 10 minutes on the first day of each 21 day cycle.

Premedication Regimen

Skin rash has been reported in patients not pretreated with a corticosteroid. Pre-treatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction. In clinical trials, dexamethasone 4 mg was given by mouth twice daily the day before, the day of, and the day after ALIMTA administration.

To reduce toxicity, patients treated with ALIMTA must be instructed to take a low-dose oral folic acid preparation or a multivitamin containing folic acid on a daily basis. At least 5 daily doses of folic acid must be taken during the 7-day period 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 one intramuscular injection of vitamin B_{12} during the week preceding the first dose of ALIMTA and every 3 cycles thereafter. Subsequent vitamin B_{12} injections may be given the same day as ALIMTA. In clinical trials, the dose of folic acid studied ranged from 350 to 1000 μg, and the dose of vitamin B_{12} received was 1000 μg. The most commonly used dose of oral folic acid was 400 μg.

Laboratory Monitoring and Dose Reduction Recommendations

Monitoring

It is recommended that patients receiving ALIMTA 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 ≥1500 cells/mm^3 and platelets ≥100,000 cells/mm^3 prior to scheduled administration of any cycle.

Dose Reduction Recommendations

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 1-3 which are suitable for using ALIMTA as a single agent or in combination with cisplatin.

Table 1. Dose Modification for ALIMTA (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 (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 version 2.0 (NCI 1998) definition of ≥CTC Grade 2 bleeding

If patients develop nonhaematologic toxicities (excluding neurotoxicity) ≥ Grade 3, treatment 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 for ALIMTA (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] NCI CTC

[b] Excluding neurotoxicity.

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

Table 3. Dose Modification for ALIMTA (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

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

Elderly Patients — In clinical trials, there has been no indication that patients 65 years of age or older are at increased risk of adverse events compared with patients younger than 65. No dose reductions other than those recommended for all patients are necessary.

Renally Impaired Patients — In clinical studies, patients with creatinine clearance of at least 45 mL/min required no dose adjustments other than those recommended for all patients. Insufficient numbers of patients with creatinine clearance below 45 mL/min have been treated to make dosage recommendations for this group of patients. Therefore, patients should not receive ALIMTA whose creatinine clearance is <45 mL/min [using the standard Cockcroft and Gault formula or GFR measured by Tc99m-DPTA serum clearance method].

Preparation and administration instructions: Use aseptic technique.

Reconstitution and further dilution prior to intravenous infusion is only recommended with 0.9% Sodium Chloride Injection. ALIMTA is physically incompatible with diluents containing calcium, including Lactated Ringer's Injection and Ringer's Injection. Coadministration of ALIMTA with other drugs and diluents has not been studied, and therefore is not recommended.

1. Use appropriate aseptic technique during the reconstitution and further dilution of ALIMTA for intravenous infusion administration.
2. Calculate the dose and the number of ALIMTA vials needed. A 500 mg vial contains 500 mg of pemetrexed. A 100 mg vial contains 100 mg of pemetrexed. The vial contains an excess of pemetrexed to facilitate delivery of label amount.
3. Prior to administration, reconstitute 500 mg vials with 20 mL of 0.9% Sodium Chloride Injection to give a solution containing 25 mg/mL pemetrexed. Reconstitute 100 mg vials with 4.2 mL of 0.9% Sodium Chloride Injection to give a solution containing 25 mg/mL pemetrexed.
4. Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in colour from colourless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted ALIMTA solution is between 6.6 and 7.8. FURTHER DILUTION IS REQUIRED.
5. The appropriate volume of reconstituted ALIMTA solution should be further diluted to 100 mL with 0.9% Sodium Chloride Injection and administered as an intravenous infusion over 10 minutes.
6. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Chemical and physical stability of reconstituted and infusion solutions of ALIMTA was demonstrated for up to 24 hours after reconstitution of the original vial when refrigerated between 2 to 8°C. However, because ALIMTA and the recommended diluent contain no antimicrobial preservatives, to reduce antimicrobial hazard, reconstituted and infusion solutions should be used immediately. Discard any unused portion.

4.3 CONTRAINDICATIONS

ALIMTA is contraindicated in patients who have a history of severe hypersensitivity reaction to pemetrexed or to any excipients in this product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

ALIMTA can suppress bone marrow function as manifested by anaemia, neutropenia, thrombocytopenia, or pancytopenia. (see section **4.8 Adverse effects (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 ≥ 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 nonhaematologic toxicity seen in the previous cycle (see section **4.2 DOSE AND METHOD OF ADMINISTRATION**, **Dose Reduction Recommendations**).

Patients treated with ALIMTA must be instructed to take folic acid and vitamin B12 with ALIMTA as a prophylactic measure to reduce treatment related toxicity (see section 4.2 **Dose and method of administration**). In the Phase 3 mesothelioma EMPHACIS trial, less overall toxicity and reductions 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 B_{12} was administered.

Serious renal events, including acute renal failure, have been reported with pemetrexed alone or in association with other chemotherapeutic agents. Many of the patients in whom these occurred had underlying risk factors for the development of renal events including dehydration or pre-existing hypertension or diabetes.

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

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

Immunodepressed status is common in cancer patients. As a result, concomitant use of live attenuated vaccines is not recommended

Cases of radiation pneumonitis have been reported in patients treated with radiation either prior, during or subsequent to their pemetrexed therapy. Particular attention should be paid to these patients and caution exercised with use of other radiosensitising agents. Cases of radiation recall have been reported in patients who received radiotherapy weeks or years previously.

Use in hepatic impairment

ALIMTA is not extensively metabolised by the liver. However, patients with hepatic impairment such as bilirubin >1.5 times the upper limit of normal (ULN) or aminotransferase >3 times the ULN (hepatic metastases absent) or >5 time the ULN (hepatic metastases present) have not been specifically studied.

ALIMTA should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available. Treatment-related adverse events of ALIMTA seen in clinical trials have been reversible. Skin rash has been reported in patients not pretreated with a corticosteroid in clinical trials. Pre-treatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction (see section **4.2 Dose and method of administration**).

The effect of third space fluid, such as pleural effusion and 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.

Use in renal impairment

ALIMTA is primarily eliminated unchanged by renal excretion. Insufficient numbers of patients have been studied with creatinine clearance below 45 mL/min. Therefore, ALIMTA should not be administered to patients whose creatinine clearance is <45 mL/min (see section **4.2 DOSE AND METHOD OF ADMINISTRATION**, **Dose Reduction Recommendations**).

Use in the elderly

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

Paediatric use

LIMTA 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

Effects on laboratory tests

There are no data available that shows that pemetrexed has an effect on laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

ALIMTA is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. In vitro studies indicate that pemetrexed is actively secreted by the organic anion transporter 3 (OAT3) in the kidney. In Vitro work also indicates that pemetrexed has affinity for OAT4 but the role of OAT4 in the renal elimination of molecules in not fully understood. Concomitant administration of nephrotoxic drugs and/or substances that are tubularly secreted could result in delayed clearance of ALIMTA.

Results from *in vitro* studies with human liver microsomes suggest that ALIMTA would not cause clinically significant interactions with drugs metabolised by CYP3A, CYP2D6, CYP2C9, and CYP1A2.

The pharmacokinetics of ALIMTA are not influenced by oral folic acid and intramuscular vitamin B12 supplementation or by concurrently administered cisplatin. Total platinum clearance is not affected by ALIMTA administration.

Although NSAIDs in moderate doses can be administered with ALIMTA in patients with normal renal function (creatinine clearance ≥80 mL/min), renal clearance was reduced by 16% when ibuprofen was concurrently administered with pemetrexed in patients with

normal renal function. Caution should be used when administering NSAIDs concurrently with ALIMTA to patients with mild to moderate renal insufficiency (creatinine clearance of 45-79 mL/min). It is recommended that patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of, and 2 days following administration of ALIMTA.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Administration of pemetrexed to male mice at intraperitoneal doses of ≥ 0.3 mg/m^2/day resulted in reproductive toxicity characterised by reduced fertility, hypospermia, and testicular atrophy.

Use in pregnancy

Pregnancy category D

The use of ALIMTA should be avoided in pregnant women because of the potential hazard to the foetus. Pemetrexed was teratogenic (causing cleft palate) in mice at intravenous doses of ≥ 15 mg/m^2/day. Other embryofetal toxic effects (embryofetal deaths, reduced fetal weights and incomplete ossification) were also observed. Embryofetal toxicity was observed at the lowest dose tested (0.6 mg/m^2/day).

Use in lactation

It is not known whether pemetrexed is excreted in human milk. Therefore, breast-feeding should 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Single agent ALIMTA (NSCLC):

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	Very Common	Rash/ desquamation	14.0	0.0	6.2	0.0
Tissue Disorders	Common	Pruritis	6.8	0.4	1.8	0.0
		Alopecia	6.4	0.4**	37.7	2.2**

* Refer to National Cancer Institute Common Toxicity (NCI CTC) Criteria for lab values for each Grade of toxicity (version 2.0).

** According to NCI CTC Criteria (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 (MPM):

Table 5 provides the frequency and severity of undesirable effects that have been reported in >5% of 168 patients with mesothelioma who were randomly assigned to receive cisplatin and ALIMTA and 163 patients with mesothelioma randomly assigned to receive single agent cisplatin. In both treatment arms, these chemonaive 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	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
		Genitourinary Other	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 2.0) 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 Criteria (version 2.0), alopecia and taste disturbance 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 and cisplatin).

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

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

Combination with cisplatin (NSCLC)

Table 6 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 B_{12}.

Table 6.

System Organ Class	Frequency	Event*	ALIMTA/cisplatin (N=839)		Gemcitabine/ Cisplatin (N=830)	
			All Grades Toxicity (%)	Grade 3 - 4 Toxicity (%)	All Grades Toxicity (%)	Grade 3 - 4 Toxicity (%)
Blood and Lymphatic System Disorders	Very Common	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 and urinary Disorders	Very Common	Creatinine increased	10.1*	0.8	6.9*	0.5
Skin and Subcutaneous	Very Common	Alopecia	11.9*	0***	21.4*	0.5***
Tissue disorder	Common	Rash/ desquamation	6.6	0.1	8.0	0.5

*P-values <0.05 comparing pemetrexed/cisplatin to gemcitabine/cisplatin, using Fisher Exact test

**Refer to NCI CTC Criteria (version 2.0) for each Grade of toxicity.

*** According to NCI CTC Criteria (version 2.0), alopecia and taste disturbance 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. Acute renal failure was observed more commonly in the pemetrexed/cisplatin arm (6 cases, 0.7%) than in the gemcitabine/cisplatin arm (0 cases).

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 (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
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.

Safety was assessed for patients who were randomised to receive pemetrexed (N=800). The incidence of adverse reactions was evaluated for patients who received ≤ 6 cycles of pemetrexed maintenance (N=519), and compared to patients who received > 6 cycles of pemetrexed (N=281). Increases in adverse reactions (all grades) were observed with longer exposure. A significant increase in the incidence of possibly study drug-related Grade 3-4 neutropenia was observed with longer exposure to pemetrexed (≤6 cycles: 3.3%, >6 cycles: 6.4%, p=0.046). No statistically significant differences in any other individual Grade 3/4/5 adverse reactions were seen with longer exposure.

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 Disorders – 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.

Hepatobiliary Disorders - Rare cases of hepatitis, potentially serious, have been reported during clinical trials with ALIMTA.

Rare: ≤0.1% of patients treated with ALIMTA

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Reported symptoms of ALIMTA 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.

If overdose occurs, general supportive measures should be instituted as deemed necessary by the treating physician. Management of ALIMTA overdose should include consideration of the use of leucovorin or thymidine rescue.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pemetrexed is an antifolate antineoplastic agent. *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 that are essential for cell replication. Both the reduced folate carrier and membrane folate binding protein transport systems appear to be involved in transport of pemetrexed into cells. Once in the cell, pemetrexed is converted to polyglutamate forms by the enzyme folyl polyglutamate synthetase. The polyglutamate forms are even more potent inhibitors of TS and GARFT than pemetrexed. Polyglutamation is a time and concentration dependent process that occurs in tumour cells and, to a lesser extent, in normal tissues. Polyglutamated metabolites have a longer intracellular half-life than the parent drug, resulting in prolonged drug action in malignant cells. Data indicates that overexpression of thymidylate synthase (TS) correlates with reduced sensitivity to pemetrexed in antifolate-resistant cell lines. Results in a study with specimens from chemonaive patients with 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.

An *in vitro* study with the MSTO-211H mesothelioma cell line showed synergistic effects when pemetrexed was combined with cisplatin.

Clinical trials

Malignant Pleural Mesothelioma

The safety and efficacy of ALIMTA have been evaluated in chemonaive patients with malignant pleural mesothelioma (MPM) as a single-agent and in combination with platinum-based regimens.

EMPHACIS, a multicentre, randomised, single-blind phase 3 study of ALIMTA plus cisplatin versus cisplatin in chemonaive patients with malignant pleural mesothelioma, has shown that patients treated with ALIMTA and cisplatin had a clinically meaningful 2.8-month median survival advantage over patients receiving cisplatin alone. ALIMTA was administered intravenously over 10 minutes at a dose of 500 mg/m^2 and cisplatin was administered

intravenously over 2 hours at a dose of 75 mg/m^2 beginning approximately 30 minutes after the end of administration of ALIMTA. Both drugs were given on Day 1 of each 21-day cycle. On this study, treatment was administered up to 6 cycles. Additional cycles were permitted for patients who were receiving benefit from therapy.

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).

Table 8 summarises the efficacy results for all patients regardless of vitamin supplementation status and those patients receiving vitamin supplementation from the time of enrolment in the trial.

Table 8. Efficacy of ALIMTA plus Cisplatin vs. Cisplatin in Malignant Pleural Mesothelioma

Efficacy Parameter	Randomised and Treated Patients		Fully Supplemented Patients	
	ALIMTA/ cis (N=226)	Cisplatin (N=222)	ALIMTA/cis (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)
Hazard ratio	0.77		0.75	
Log Rank p-value*	0.020		0.051	
Percent censored	35.8	28.4	43.5	36.8
Median Time to Tumor 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)
Hazard ratio	0.68		0.64	
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)
Hazard ratio	0.61		0.57	
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	

*p-value refers to comparison between arms.

**Time to treatment failure was defined as the time from study enrolment to the first observation of disease progression, death because of any cause, or discontinuation because of any other reason.

***In the ALIMTA/cis arm, randomised and treated (N=225) and fully supplemented (N=167).

Table 9 summarises the number of cycles of treatment completed by randomised and treated patients and fully supplemented patients. Patients who never received folic acid and vitamin B_{12} during study therapy received a median of 2 cycles in both treatment arms.

Table 9. Summary of Cycles Given

	Randomised and Treated Patients		Fully Supplemented Patients	
Cycle Statistics	ALIMTA/cis (N=226)	Cisplatin (N=222)	ALIMTA/cis (N=168)	Cisplatin (N=163)
Median Cycles Completed	6.0	4.0	6.0	4.0
Range	(1-12)	(1-9)	(1-12)	(1-9)
Total Cycles Completed	1066	877	825	650
Cycles given at full dosage (%)	1030 (96.6%)	874 (99.7%)	802 (97.2%)	648 (99.7%)

A statistically significant improvement of the clinically relevant symptoms (pain and dyspnoea) associated with malignant pleural mesothelioma in the ALIMTA/cisplatin arm (212 patients) versus the cisplatin arm alone (218 patients) was demonstrated using the Lung Cancer Symptom Scale (LCCS). By the end of treatment (after 6 cycles), there was a statistically significant difference in favour of ALIMTA/cis for the symptoms of dyspnoea, pain, fatigue, symptom distress, interference with activity, and total LCSS. Statistically significant differences in pulmonary function tests were also observed. Differences favouring the ALIMTA/cis arm were seen in all pulmonary function tests early in therapy; these differences were occasionally significant in early cycles but uniformly became significant in later cycles. The separation between the treatment arms was achieved by improvement in lung function in the ALIMTA/cis arm and deterioration of lung function over time in the control arm.

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 (for up to 6 cycles) in chemonaive patients with locally advanced or metastatic (Stage IIIb or IV) non-small cell lung cancer (NSCLC) showed that ALIMTA plus cisplatin (Intent-To-Treat [ITT] population n = 862) met its primary endpoint and showed similar clinical efficacy as gemcitabine plus cisplatin (ITT n = 863) in overall survival (adjusted hazard ratio 0.94; 95% CI 0.84-1.05). Refer to following figure.

Figure 1. Kaplan-Meier Curve for Overall Survival - ALIMTA + Cisplatin (AC) vs. Gemcitabine + Cisplatin (GC) in First-line Non-Small Cell Lung Cancer – ITT Population

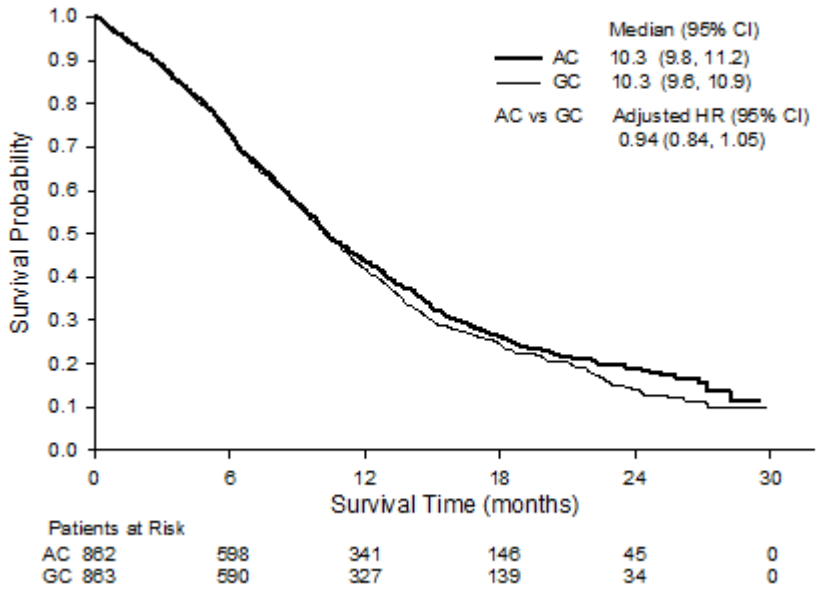


Table 10. Efficacy of ALIMTA + Cisplatin vs. Gemcitabine + Cisplatin in First-line Non-Small Cell Lung Cancer – ITT Population

	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%

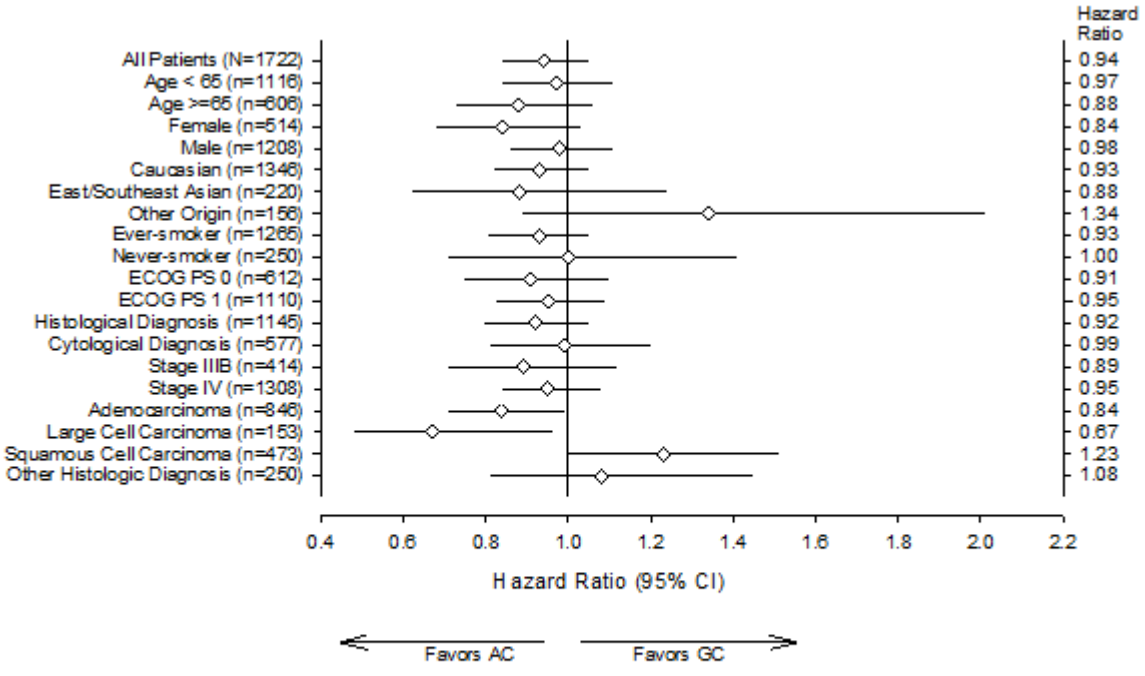
Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent to treat; n = total population size; mos = months.

[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 as shown in the following figure:

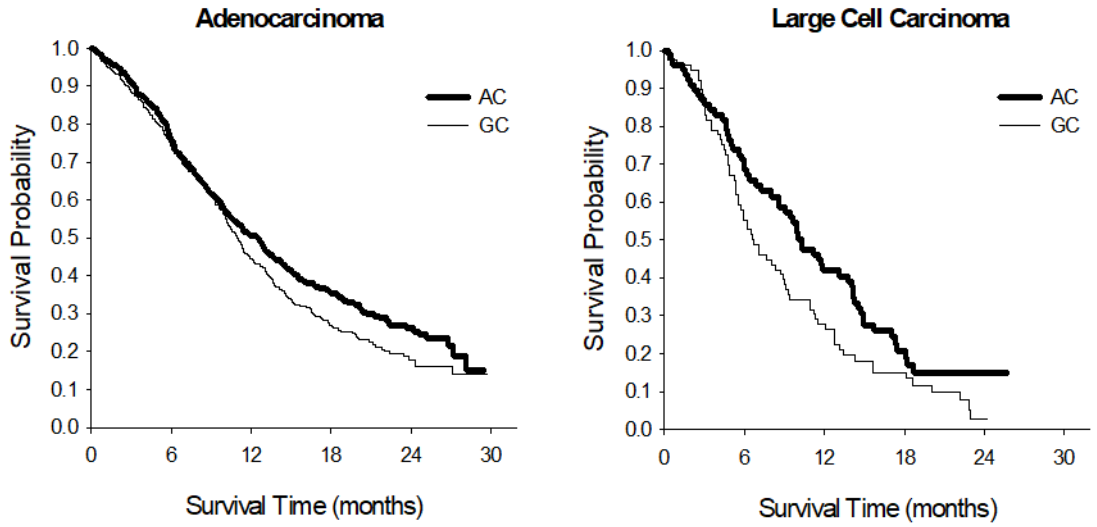
Figure 2. Forest Plot for Overall Survival Adjusted Hazard Ratios of Subgroups ALIMTA + Cisplatin vs. Gemcitabine + Cisplatin in First-line Non-Small Cell Lung Cancer – ITT Population



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). The results of the analysis of overall survival in patients with adenocarcinoma and large cell carcinoma are shown in the figures below:

Figure 3. Kaplan-Meier Curves for Overall Survival - ALIMTA + Cisplatin (AC) vs. Gemcitabine + Cisplatin (GC) in First-line Non-Small Cell Lung Cancer – Adenocarcinoma and Large Cell Carcinoma



On this study, treatment was administered up to 6 cycles.

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

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.

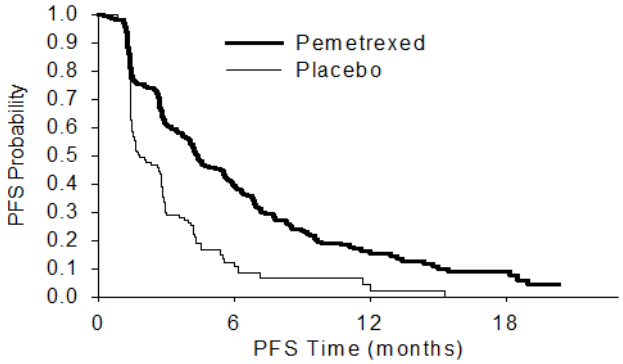
In the overall study population, ALIMTA was statistically superior to placebo in terms of overall survival (OS) (median 13.4 months versus 10.6 months, HR=0.79 (95% CI: 0.65-0.95), p-value=0.012) and PFS (median 4.0 months versus 2.0 months, HR=0.60 (95% CI: 0.49-0.73), p-value<0.00001). Consistent with 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.

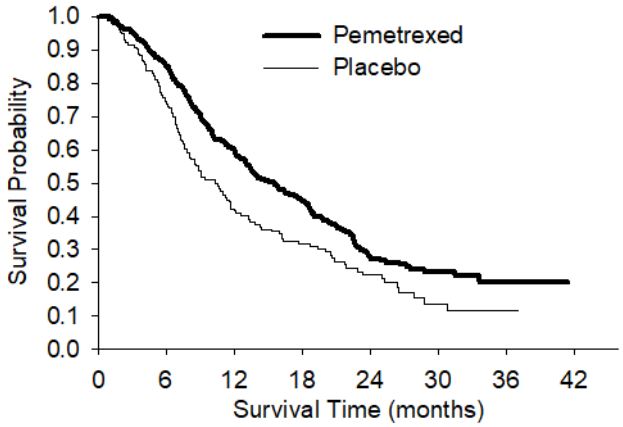
There were no clinically relevant differences observed for the safety profile of ALIMTA within the histology subgroups.

Figure 4. 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

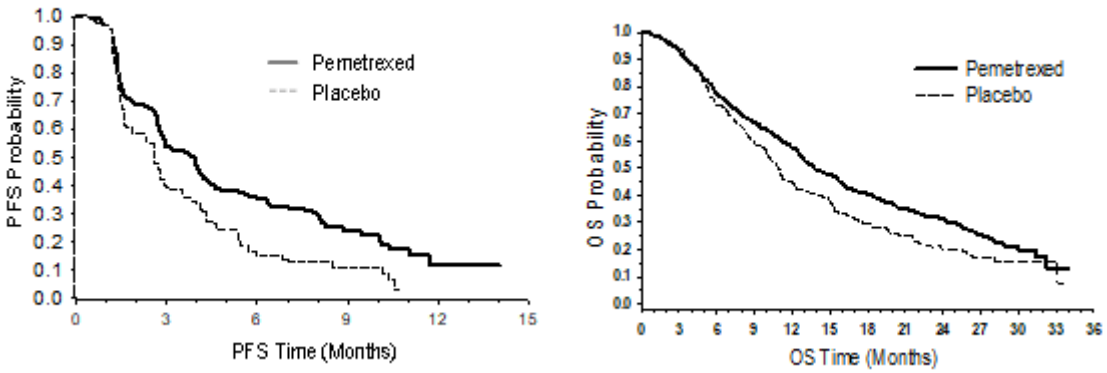
induction therapy to the start of maintenance treatment was 2.96 months on both the ALIMTA arm and the placebo arm. Randomised patients received maintenance treatment until disease progression. For statistical purposes, efficacy and safety were measured from the time of randomisation after completion 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 ratio = 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.

Figure 5. 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 (with treatment until progression) 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 11, indicate comparable efficacy between pemetrexed and docetaxel.

Table 11. 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.

On this study, treatment was administered until disease progression

An analysis of the impact of NSCLC histology on overall survival was in favor of ALIMTA versus docetaxel for other than predominantly squamous histology (n=399, 9.3 versus 8.0 months, adjusted HR = 0.78; 95% CI =0 .61-1.00, p =0.047) and was in favor of docetaxel for squamous cell carcinoma histology (n=172, 6.2 versus 7.4 months, adjusted HR = 1.56; 95% CI =1.08-2.26, p =0.018). There were no clinically relevant differences observed for the safety profile of ALIMTA within the histology subgroups.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

ALIMTA is for intravenous administration only.

Distribution

ALIMTA has a steady state volume of distribution of 16.1 litres. In vitro studies indicate that ALIMTA is approximately 81% bound to plasma proteins. Binding is not affected by degree of renal impairment.

Metabolism

ALIMTA undergoes limited hepatic metabolism.

Excretion

ALIMTA is primarily eliminated in the urine with up to 70% to 90% of the dose recovered unchanged within the first 24 hours following administration. Total plasma clearance of ALIMTA is 92 mL/min, and the elimination half life from plasma is 3.5 hours in patients with normal renal function.

Special Populations

Analyses to evaluate the pharmacokinetics of ALIMTA in special populations included 287 patients with a variety of advanced tumor types from 10 single agent Phase 2 studies, 70 patients from the Phase 3 malignant pleural mesothelioma EMPHACIS trial, and 47 patients from a Phase 1 renal study.

Elderly

No effect of age on the pharmacokinetics of ALIMTA was observed over a range of 26 to 80 years.

Hepatic Insufficiency

No effect of AST (SGOT), ALT (SGPT), or total bilirubin on the pharmacokinetics of ALIMTA was observed. However, specific studies of hepatically impaired patients have not been conducted (see section **4.4 Special warnings and precautions for use**).

Renal Insufficiency

Pharmacokinetic analyses included 127 patients with reduced renal function. Total plasma clearance and renal clearance of ALIMTA decrease as renal function decreases. On average, patients with creatinine clearance of 45 mL/min will have a 56% increase in ALIMTA total systemic exposure (AUC) relative to patients with creatinine clearance of 90 mL/min (see section **4.4 Special warnings and precautions for use** and section **4.2 Dose and method of administration**).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Pemetrexed has been shown to be clastogenic in the *in vivo* micronucleus assay in the mouse, but was negative in the *in vitro* chromosome aberration test in Chinese hamster ovary cells. Pemetrexed was negative in assays for gene mutation (bacteria and mammalian cells *in vitro*).

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each 500 mg vial of ALIMTA contains 500 mg of mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

Each 100 mg vial of ALIMTA contains 106.4 mg of mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF-LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. ALIMTA is not light sensitive.

6.5 NATURE AND CONTENTS OF CONTAINER

ALIMTA, pemetrexed disodium for injection is available in sterile single-use vials containing 100 mg or 500 mg pemetrexed (pack size 1 vial).

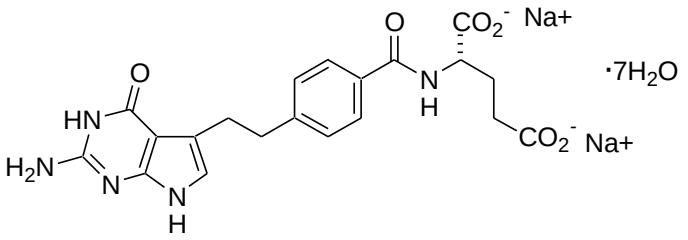
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The active ingredient in ALIMTA powder for injection is pemetrexed disodium. Pemetrexed disodium has the chemical name l-glutamic acid, *N*-[4-[2-(2-amino-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate. It has an empirical formula of $C_{20}H_{19}N_5O_6 \bullet 2Na \bullet 7H_2O$ and a molecular weight of 597.49. Pemetrexed disodium is a white to almost white solid. The structural formula is as follows:



CAS number

The CAS number for pemetrexed disodium heptahydrate is 357166-29-1.

7. MEDICINE SCHEDULE

S4 – Prescription only Medicine

8. SPONSOR

Eli Lilly Australia Pty. Ltd

Level 9, 60 Margaret Street, Sydney, NSW 2000 AUSTRALIA

1800 454 559

9. DATE OF FIRST APPROVAL

30 June 2004

10. DATE OF REVISION

13 September 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Sponsor address update