HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ALIMTA safely and effectively. See full prescribing information for ALIMTA.

ALIMTA (pemetrexed for injection) Lyophilized Powder, for Solution for Intravenous Use

Initial U.S. Approval: 2004

RECENT MAJOR CHANGES

Dosage and Administration, Premedication Regimen and Concurrent Medications (2.3)	10/2012
Warnings and Precautions, Requirement for Premedication and Concomitant Medication to Reduce Toxicity (5.1)	10/2012
Warnings and Precautions, Required Laboratory Monitoring (5.5)	10/2012
Warnings and Precautions, Third Space Fluid (5.7) --- removal	11/2011

INDICATIONS AND USAGE

ALIMTA® is a folate analog metabolic inhibitor indicated for:

- Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer:
  - Initial treatment in combination with cisplatin. (1.1)
  - Maintenance treatment of patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. (1.2)
  - After prior chemotherapy as a single-agent. (1.3)
- Mesothelioma: in combination with cisplatin. (1.4)

Limitations of Use:

- ALIMTA is not indicated for the treatment of patients with squamous cell non-small cell lung cancer. (1.5)

DOSAGE AND ADMINISTRATION

- Combination use in Non-Small Cell Lung Cancer and Mesothelioma: Recommended dose of ALIMTA is 500 mg/m^2 i.v. on Day 1 of each 21-day cycle in combination with cisplatin 75 mg/m^2 i.v. beginning 30 minutes after ALIMTA administration. (2.1)
- Single-Agent use in Non-Small Cell Lung Cancer: Recommended dose of ALIMTA is 500 mg/m^2 i.v. on Day 1 of each 21-day cycle. (2.2)
- Prior to initiating ALIMTA, initiate supplementation with oral folic acid and intramuscular vitamin B_{12}. Continue folic acid and vitamin B_{12} supplementation throughout treatment. Administer corticosteroids the day before, the day of, and the day after ALIMTA administration. (2.3)
- Dose Reductions: Dose reductions or discontinuation may be needed based on toxicities from the preceding cycle of therapy. (2.4)

DOSAGE FORMS AND STRENGTHS

- 100 mg vial for injection (3)
- 500 mg vial for injection (3)

CONTRAINDICATIONS

History of severe hypersensitivity reaction to pemetrexed. (4)

WARNINGS AND PRECAUTIONS

- Premedication regimen: Prior to treatment with ALIMTA, initiate supplementation with oral folic acid and intramuscular vitamin B_{12} to reduce the severity of hematologic and gastrointestinal toxicity of ALIMTA. (5.1)
- Bone marrow suppression: Reduce doses for subsequent cycles based on hematologic and nonhematologic toxicities. (5.2)
- Renal function: Do not administer when CrCl <45 mL/min. (2.4, 5.3)
- NSAIDs with renal insufficiency: Use caution in patients with mild to moderate renal insufficiency (CrCl 45-79 mL/min). (5.4)
- Lab monitoring: Do not initiate a cycle unless ANC ≥1500 cells/mm^3, platelets ≥100,000 cells/mm^3, and CrCl ≥45 mL/min. (5.5)
- Pregnancy: Fetal harm can occur when administered to a pregnant woman. Women should be advised to use effective contraception measures to prevent pregnancy during treatment with ALIMTA. (5.6)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥20%) with single-agent use are fatigue, nausea, and anorexia. Additional common adverse reactions when used in combination with cisplatin include vomiting, neutropenia, leukopenia, anemia, stomatitis/pharyngitis, thrombocytopenia, and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- NSAIDs: Use caution with NSAIDs. (7.1)
- Nephrotoxic drugs: Concomitant use of these drugs and/or substances which are tubularly secreted may result in delayed clearance. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 00/0000

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Nonsquamous Non-Small Cell Lung Cancer - Combination with Cisplatin

ALIMTA is indicated in combination with cisplatin therapy for the initial treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer.

1.2 Nonsquamous Non-Small Cell Lung Cancer - Maintenance

ALIMTA is indicated for the maintenance treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.

1.3 Nonsquamous Non-Small Cell Lung Cancer - After Prior Chemotherapy

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

1.4 Mesothelioma

ALIMTA in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.

1.5 Limitations of Use

ALIMTA is not indicated for the treatment of patients with squamous cell non-small cell lung cancer. *[see Clinical Studies (14.1, 14.2, 14.3)]*

2 DOSAGE AND ADMINISTRATION

2.1 Combination Use with Cisplatin for Nonsquamous Non-Small Cell Lung Cancer or Malignant Pleural Mesothelioma

The recommended dose of ALIMTA is 500 mg/m^2 administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle. The recommended dose of cisplatin is 75 mg/m^2 infused over 2 hours beginning approximately 30 minutes after the end of ALIMTA administration. See cisplatin package insert for more information.

2.2 Single-Agent Use as Maintenance Following First-Line Therapy, or as a Second-Line Therapy

The recommended dose of ALIMTA is 500 mg/m^2 administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle.

2.3 Premedication Regimen and Concurrent Medications

Vitamin Supplementation

Instruct patients to initiate folic acid 400 mcg to 1000 mcg orally once daily beginning 7 days before the first dose of ALIMTA. Continue folic acid during the full course of therapy and for 21 days after the last dose of ALIMTA *[see Warnings and Precautions (5.1)]*.

Administer vitamin B_{12} 1 mg intramuscularly 1 week prior to the first dose of ALIMTA and every 3 cycles thereafter. Subsequent vitamin B_{12} injections may be given the same day as treatment with ALIMTA *[see Warnings and Precautions (5.1)]*.

Corticosteroids

Administer dexamethasone 4 mg by mouth twice daily the day before, the day of, and the day after ALIMTA administration *[see Warnings and Precautions (5.1)]*.

2.4 Laboratory Monitoring and Dose Reduction/Discontinuation Recommendations

Monitoring

Complete blood cell counts, including platelet counts, should be performed on all patients receiving ALIMTA. Patients should be monitored for nadir and recovery, which were tested in the clinical study before each dose and on days 8 and 15 of each cycle. Patients should not begin a new cycle of treatment unless the ANC is ≥1500 cells/mm^3, the platelet count is ≥100,000 cells/mm^3, and creatinine clearance is ≥45 mL/min. Periodic chemistry tests should be performed to evaluate renal and hepatic function *[see Warnings and Precautions (5.5)]*.

Dose Reduction Recommendations

Dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum nonhematologic 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 Reduction for ALIMTA (single-agent or in combination) and Cisplatin - Hematologic Toxicities

Nadir ANC <500/mm^3 and nadir platelets ≥50,000/mm^3.	75% of previous dose (pemetrexed and cisplatin).
Nadir platelets <50,000/mm^3 without bleeding regardless of nadir ANC.	75% of previous dose (pemetrexed and cisplatin).
Nadir platelets <50,000/mm^3 with bleeding[a], regardless of nadir ANC.	50% of previous dose (pemetrexed and cisplatin).

[a] These criteria meet the CTC version 2.0 (NCI 1998) definition of ≥CTC Grade 2 bleeding.

If patients develop nonhematologic 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 guidelines in Table 2.

Table 2: Dose Reduction for ALIMTA (single-agent or in combination) and Cisplatin - Nonhematologic 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 diarrhea requiring hospitalization (irrespective of Grade) or Grade 3 or 4 diarrhea	75% of previous dose	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose	100% of previous dose

[a] NCI Common Toxicity Criteria (CTC).
[b] Excluding neurotoxicity (see Table 3).

In the event of neurotoxicity, the recommended dose adjustments for ALIMTA and cisplatin are described in Table 3. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is experienced.

Table 3: Dose Reduction for ALIMTA (single-agent or in combination) and Cisplatin - Neurotoxicity

CTC Grade	Dose of ALIMTA (mg/m^2)	Dose of Cisplatin (mg/m^2)
0-1	100% of previous dose	100% of previous dose
2	100% of previous dose	50% of previous dose

Discontinuation Recommendation

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

Renally Impaired Patients

In clinical studies, patients with creatinine clearance ≥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 *[see Clinical Pharmacology (12.3)]*. Therefore, ALIMTA should not be administered to patients whose creatinine clearance is <45 mL/min using the standard Cockcroft and Gault formula (below) or GFR measured by Tc99m-DPTA serum clearance method:

Males: $$\frac{[140 - \text{Age in years}] \times \text{Actual Body Weight (kg)}}{72 \times \text{Serum Creatinine (mg/dL)}} = \text{mL/min}$$

Females: Estimated creatinine clearance for males × 0.85

Caution should be exercised when administering ALIMTA concurrently with NSAIDs to patients whose creatinine clearance is <80 mL/min *[see Drug Interactions (7.1)]*.

2.5 Preparation and Administration Precautions

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions of ALIMTA. The use of gloves is recommended. If a solution of ALIMTA contacts the skin, wash the skin immediately and thoroughly with soap and water. If ALIMTA contacts the mucous membranes, flush thoroughly with water. Several published guidelines for handling and disposal of anticancer agents are available *[see References (15)]*.

ALIMTA is not a vesicant. There is no specific antidote for extravasation of ALIMTA. To date, there have been few reported cases of ALIMTA extravasation, which were not assessed as serious by the investigator. ALIMTA extravasation should be managed with local standard practice for extravasation as with other non-vesicants.

2.6 Preparation for Intravenous Infusion Administration

1. Use aseptic technique during the reconstitution and further dilution of ALIMTA for intravenous infusion administration.
2. Calculate the dose of ALIMTA and determine the number of vials needed. Vials contain either 100 mg or 500 mg of ALIMTA. The vials contain an excess of ALIMTA to facilitate delivery of label amount.
3. Reconstitute each 100-mg vial with 4.2 ml of 0.9% Sodium Chloride Injection (preservative free). Reconstitute each 500-mg vial with 20 mL of 0.9% Sodium Chloride Injection (preservative free). Reconstitution of either size vial gives a solution containing 25 mg/mL ALIMTA. Gently swirl each vial until the powder is completely dissolved. The resulting

solution is clear and ranges in color from colorless 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.

4. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulate matter is observed, do not administer.
5. An appropriate quantity of the reconstituted ALIMTA solution must be further diluted into a solution of 0.9% Sodium Chloride Injection (preservative free), so that the total volume of solution is 100 ml. ALIMTA is administered as an intravenous infusion over 10 minutes.
6. Chemical and physical stability of reconstituted and infusion solutions of ALIMTA were demonstrated for up to 24 hours following initial reconstitution, when stored refrigerated. When prepared as directed, reconstitution and infusion solutions of ALIMTA contain no antimicrobial preservatives. Discard any unused portion.

Reconstitution and further dilution prior to intravenous infusion is only recommended with 0.9% Sodium Chloride Injection (preservative free). ALIMTA is physically incompatible with diluents containing calcium, including Lactated Ringer's Injection, USP and Ringer's Injection, USP and therefore these should not be used. Coadministration of ALIMTA with other drugs and diluents has not been studied, and therefore is not recommended. ALIMTA is compatible with standard polyvinyl chloride (PVC) administration sets and intravenous solution bags.

3 DOSAGE FORMS AND STRENGTHS

ALIMTA, pemetrexed for injection, is a white to either light-yellow or green-yellow lyophilized powder available in sterile single-use vials containing 100 mg or 500 mg pemetrexed.

4 CONTRAINDICATIONS

ALIMTA is contraindicated in patients who have a history of severe hypersensitivity reaction to pemetrexed.

5 WARNINGS AND PRECAUTIONS

5.1 Requirement for Premedication and Concomitant Medication to Reduce Toxicity

Vitamin Supplementation

Prior to treatment with ALIMTA, initiate supplementation with oral folic acid and intramuscular vitamin B_{12} to reduce the severity of hematologic and gastrointestinal toxicity of ALIMTA *[see Dosage and Administration (2.3)]*. Do not substitute oral vitamin B_{12} for intramuscular vitamin B_{12}. In clinical studies, the incidence of the following Grade 3-4 toxicities were higher in patients with mesothelioma who were never supplemented as compared to patients who were fully supplemented with folic acid and vitamin B_{12} prior to and throughout ALIMTA treatment: neutropenia [38% versus 23%], thrombocytopenia [9% versus 5%], febrile neutropenia [9% versus 0.6%], and infection with neutropenia [6% versus. 0].

Corticosteroids

Administer dexamethasone the day before, the day of, and the day after ALIMTA administration *[see Dosage and Administration (2.3)]*.

5.2 Bone Marrow Suppression

ALIMTA can suppress bone marrow function, as manifested by neutropenia, thrombocytopenia, and anemia (or pancytopenia) *[see Adverse Reactions (6.1)]*; myelosuppression is usually the dose-limiting toxicity. Dose reductions for subsequent cycles are based on nadir ANC, platelet count, and maximum nonhematologic toxicity seen in the previous cycle *[see Dosage and Administration (2.4)]*.

5.3 Decreased Renal Function

ALIMTA is primarily eliminated unchanged by renal excretion. No dosage adjustment is needed in patients with creatinine clearance ≥45 mL/min. Insufficient numbers of patients have been studied with creatinine clearance <45 mL/min to give a dose recommendation. Therefore, ALIMTA should not be administered to patients whose creatinine clearance is <45 mL/min *[see Dosage and Administration (2.4)]*.

One patient with severe renal impairment (creatinine clearance 19 mL/min) who did not receive folic acid and vitamin B_{12} died of drug-related toxicity following administration of ALIMTA alone.

5.4 Use with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) with Mild to Moderate Renal Insufficiency

Caution should be used when administering NSAIDs concurrently with ALIMTA to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min) *[see Drug Interactions (7.1)]*.

5.5 Required Laboratory Monitoring

Obtain a complete blood count and renal function tests at the beginning of each cycle and as needed. Do not initiate a cycle of treatment unless the ANC is ≥1500 cells/mm^3, the platelet count is ≥100,000 cells/mm^3, and creatinine clearance is ≥45 mL/min *[see Dosage and Administration (2.4)]*.

5.6 Pregnancy Category D

Based on its mechanism of action, ALIMTA can cause fetal harm when administered to a pregnant woman. Pemetrexed administered intraperitoneally to mice during organogenesis was embryotoxic, fetotoxic and teratogenic in mice at greater than 1/833rd the recommended human dose. If ALIMTA is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid

becoming pregnant. Women should be advised to use effective contraceptive measures to prevent pregnancy during treatment with ALIMTA *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.

In clinical trials, the most common adverse reactions (incidence ≥20%) during therapy with ALIMTA as a single-agent were fatigue, nausea, and anorexia. Additional common adverse reactions (incidence ≥20%) during therapy with ALIMTA when used in combination with cisplatin included vomiting, neutropenia, leukopenia, anemia, stomatitis/pharyngitis, thrombocytopenia, and constipation.

Non-Small Cell Lung Cancer (NSCLC) - ALIMTA in Combination with Cisplatin

Table 4 provides the frequency and severity of adverse reactions that have been reported in >5% of 839 patients with NSCLC who were randomized to study and received ALIMTA plus cisplatin and 830 patients with NSCLC who were randomized to study and received gemcitabine plus cisplatin. 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 4: Adverse Reactions in Fully Supplemented Patients Receiving ALIMTA plus Cisplatin in NSCLC[a]

Reaction[b]	ALIMTA/cisplatin (N=839)		Gemcitabine/cisplatin (N=830)	
	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)
All Adverse Reactions	90	37	91	53
Laboratory				
Hematologic				
Anemia	33	6	46	10
Neutropenia	29	15	38	27
Leukopenia	18	5	21	8
Thrombocytopenia	10	4	27	13
Renal				
Creatinine elevation	10	1	7	1
Clinical				
Constitutional Symptoms				
Fatigue	43	7	45	5
Gastrointestinal				
Nausea	56	7	53	4
Vomiting	40	6	36	6
Anorexia	27	2	24	1
Constipation	21	1	20	0
Stomatitis/Pharyngitis	14	1	12	0
Diarrhea	12	1	13	2
Dyspepsia/Heartburn	5	0	6	0
Neurology				
Neuropathy-sensory	9	0	12	1
Taste disturbance	8	0[c]	9	0[c]
Dermatology/Skin				
Alopecia	12	0[c]	21	1[c]
Rash/Desquamation	7	0	8	1

[a] 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.

[b] Refer to NCI CTC Criteria version 2.0 for each Grade of toxicity.

[c] According to NCI CTC Criteria version 2.0, this adverse event term should only be reported as Grade 1 or 2.

No clinically relevant differences in adverse reactions were seen in patients based on histology.

In addition to the lower incidence of hematologic toxicity on the ALIMTA and cisplatin arm, use of transfusions (RBC and platelet) and hematopoietic growth factors was lower in the ALIMTA and cisplatin arm compared to the gemcitabine and cisplatin arm.

The following additional adverse reactions were observed in patients with non-small cell lung cancer randomly assigned to receive ALIMTA plus cisplatin.

Incidence 1% to 5%

Body as a Whole — febrile neutropenia, infection, pyrexia
General Disorders — dehydration
Metabolism and Nutrition — increased AST, increased ALT
Renal — creatinine clearance decrease, renal failure
Special Senses — conjunctivitis

Incidence Less than 1%

Cardiovascular — arrhythmia
General Disorders — chest pain
Metabolism and Nutrition — increased GGT
Neurology — motor neuropathy

Non-Small Cell Lung Cancer (NSCLC) - Maintenance

ALIMTA Maintenance Following Non-ALIMTA Containing, Platinum-Based Induction Therapy

Table 5 provides the frequency and severity of adverse reactions reported in >5% of the 438 patients with NSCLC who received ALIMTA maintenance and the 218 patients with NSCLC who received placebo following a platinum-based induction therapy.

All patients received study therapy immediately following 4 cycles of platinum-based treatment for locally advanced or metastatic NSCLC. Patients in both study arms were fully supplemented with folic acid and vitamin B_{12}.

Table 5: Adverse Reactions in Patients Receiving ALIMTA versus Placebo in NSCLC[a] Following Platinum-Based Induction Therapy

Reaction[b]	ALIMTA (N=438)		Placebo (N=218)	
	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)
All Adverse Reactions	66	16	37	4
Laboratory				
Hematologic				
Anemia	15	3	6	1
Neutropenia	6	3	0	0
Leukopenia	6	2	1	1
Hepatic				
Increased ALT	10	0	4	0
Increased AST	8	0	4	0
Clinical				
Constitutional Symptoms				
Fatigue	25	5	11	1
Gastrointestinal				
Nausea	19	1	6	1
Anorexia	19	2	5	0
Vomiting	9	0	1	0
Mucositis/stomatitis	7	1	2	0
Diarrhea	5	1	3	0
Infection	5	2	2	0
Neurology				
Neuropathy-sensory	9	1	4	0
Dermatology/Skin				
Rash/Desquamation	10	0	3	0

[a] 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.

[b] Refer to NCI CTCAE Criteria version 3.0 for each Grade of toxicity.

No clinically relevant differences in Grade 3/4 adverse reactions were seen in patients based on age, gender, ethnic origin, or histology except a higher incidence of Grade 3/4 fatigue for Caucasian patients compared to non-Caucasian patients (6.5% versus 0.6%).

Safety was assessed by exposure for patients who received at least one dose of ALIMTA (N=438). The incidence of adverse reactions was evaluated for patients who received ≤6 cycles of ALIMTA, and compared to patients who received >6 cycles of ALIMTA. Increases in adverse reactions (all grades) were observed with longer exposure; however no clinically relevant differences in Grade 3/4 adverse reactions were seen.

Consistent with the higher incidence of anemia (all grades) on the ALIMTA arm, use of transfusions (mainly RBC) and erythropoiesis stimulating agents (ESAs; erythropoietin and darbepoetin) were higher in the ALIMTA arm compared to the placebo arm (transfusions 9.5% versus 3.2%, ESAs 5.9% versus 1.8%).

The following additional adverse reactions were observed in patients with non-small cell lung cancer who received ALIMTA.

Incidence 1% to 5%

Dermatology/Skin — alopecia, pruritis/itching
Gastrointestinal — constipation
General Disorders — edema, fever (in the absence of neutropenia)
Hematologic — thrombocytopenia
Renal — decreased creatinine clearance, increased creatinine, decreased glomerular filtration rate
Special Senses — ocular surface disease (including conjunctivitis), increased lacrimation

Incidence Less than 1%

Cardiovascular — supraventricular arrhythmia
Dermatology/Skin — erythema multiforme
General Disorders — febrile neutropenia, allergic reaction/hypersensitivity
Neurology — motor neuropathy
Renal — renal failure

Continuation of ALIMTA as Maintenance Following ALIMTA Plus Platinum Induction Therapy

Table 6 provides the frequency and severity of adverse reactions reported in >5% of the 500 patients with non-squamous NSCLC who received at least one cycle of ALIMTA maintenance (n=333) or placebo (n=167) on the continuation maintenance trial.

The median of maintenance cycles administered to patients receiving one or more doses of maintenance therapy was 4 on both the pemetrexed and placebo arms. Dose reductions for adverse events occurred in 3.3% of patients in the ALIMTA arm and 0.6% in the placebo arm. Dose delays for adverse events occurred in 22% of patients in the ALIMTA arm and 16% in the placebo arm. Patients in both study arms were supplemented with folic acid and vitamin B_{12}.

Table 6: Selected[a] Adverse Reactions[b] Occurring in ≥5% of Patients Receiving ALIMTA in Nonsquamous NSCLC Following ALIMTA Plus Cisplatin Induction Therapy

Adverse Reaction Organ System and Term	ALIMTA (N=333)		Placebo (N=167)	
	All Grades[a] Toxicity (%)	Grade 3-4[a] Toxicity (%)	All Grades[a] Toxicity (%)	Grades 3-4[a] Toxicity (%)
All Adverse Reactions	53	17	34	4.8
Laboratory				
Hematologic				
Anemia	15	4.8	4.8	0.6
Neutropenia	9	3.9	0.6	0
Clinical				
Constitutional Symptoms				
Fatigue	18	4.5	11	0.6
Gastrointestinal				
Nausea	12	0.3	2.4	0
Vomiting	6	0	1.8	0
Mucositis/stomatitis	5	0.3	2.4	0
General Disorders				
Edema	5	0	3.6	0

[a] Adverse reactions of any severity (all grades) occurring more frequently (≥5%) or Grade 3-4 adverse reactions occurring more frequently (≥2%) in ALIMTA-treated patients compared to those receiving placebo.
[b] NCI CTCAE Criteria version 3.0

Administration of RBC (13% versus 4.8%) and platelet (1.5% versus 0.6%) transfusions, erythropoiesis stimulating agents (12% versus 7%), and granulocyte colony stimulating factors (6% versus 0) were higher in the ALIMTA arm compared to the placebo arm.

The following additional Grade 3 or 4 adverse reactions were observed more frequently in the ALIMTA arm.

Incidence 1% to 5%

Blood/Bone Marrow — thrombocytopenia
General Disorders — febrile neutropenia

Incidence Less than 1%

Cardiovascular — ventricular tachycardia, syncope
General Disorders — pain

Gastrointestinal — gastrointestinal obstruction
Neurologic — depression
Renal — renal failure
Vascular — pulmonary embolism

Non-Small Cell Lung Cancer (NSCLC) – After Prior Chemotherapy

Table 7 provides the frequency and severity of adverse reactions that have been reported in >5% of 265 patients randomly assigned to receive single-agent ALIMTA with folic acid and vitamin B_{12} supplementation and 276 patients randomly assigned to receive single-agent docetaxel. All patients were diagnosed with locally advanced or metastatic NSCLC and received prior chemotherapy.

Table 7: Adverse Reactions in Fully Supplemented Patients Receiving ALIMTA versus Docetaxel in NSCLC[a]

Reaction[b]	ALIMTA (N=265)		Docetaxel (N=276)	
	All Grades Toxicity (%)	Grades 3-4 Toxicity (%)	All Grades Toxicity (%)	Grades 3-4 Toxicity (%)
Laboratory				
Hematologic				
Anemia	19	4	22	4
Leukopenia	12	4	34	27
Neutropenia	11	5	45	40
Thrombocytopenia	8	2	1	0
Hepatic				
Increased ALT	8	2	1	0
Increased AST	7	1	1	0
Clinical				
Gastrointestinal				
Nausea	31	3	17	2
Anorexia	22	2	24	3
Vomiting	16	2	12	1
Stomatitis/Pharyngitis	15	1	17	1
Diarrhea	13	0	24	3
Constipation	6	0	4	0
Constitutional Symptoms				
Fatigue	34	5	36	5
Fever	8	0	8	0
Dermatology/Skin				
Rash/Desquamation	14	0	6	0
Pruritis	7	0	2	0
Alopecia	6	1[c]	38	2[c]

[a] 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.
[b] Refer to NCI CTC Criteria for lab values for each Grade of toxicity (version 2.0).
[c] According to NCI CTC Criteria version 2.0, this adverse event term should only be reported as Grade 1 or 2.

No clinically relevant differences in adverse reactions were seen in patients based on histology.

Clinically relevant adverse reactions occurring in <5% of patients that received ALIMTA treatment but >5% of patients that received docetaxel include CTC Grade 3/4 febrile neutropenia (1.9% ALIMTA, 12.7% docetaxel).

The following additional adverse reactions were observed in patients with non-small cell lung cancer randomly assigned to receive ALIMTA.

Incidence 1% to 5%

Body as a Whole — abdominal pain, allergic reaction/hypersensitivity, febrile neutropenia, infection
Dermatology/Skin — erythema multiforme
Neurology — motor neuropathy, sensory neuropathy
Renal — increased creatinine

Incidence Less than 1%

Cardiovascular — supraventricular arrhythmias

Malignant Pleural Mesothelioma (MPM)

Table 8 provides the frequency and severity of adverse reactions 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 8: Adverse Reactions in Fully Supplemented Patients Receiving ALIMTA plus Cisplatin in MPM[a]

Reaction[b]	ALIMTA/cisplatin (N=168)		Cisplatin (N=163)	
	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)
Laboratory				
Hematologic				
Neutropenia	56	23	13	3
Leukopenia	53	15	17	1
Anemia	26	4	10	0
Thrombocytopenia	23	5	9	0
Renal				
Creatinine elevation	11	1	10	1
Creatinine clearance decreased	16	1	18	2
Clinical				
Eye Disorder				
Conjunctivitis	5	0	1	0
Gastrointestinal				
Nausea	82	12	77	6
Vomiting	57	11	50	4
Stomatitis/Pharyngitis	23	3	6	0
Anorexia	20	1	14	1
Diarrhea	17	4	8	0
Constipation	12	1	7	1
Dyspepsia	5	1	1	0
Constitutional Symptoms				
Fatigue	48	10	42	9
Metabolism and Nutrition				
Dehydration	7	4	1	1
Neurology				
Neuropathy-sensory	10	0	10	1
Taste Disturbance	8	0[c]	6	0[c]
Dermatology/Skin				
Rash	16	1	5	0
Alopecia	11	0[c]	6	0[c]

[a] 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.

[b] Refer to NCI CTC Criteria version 2.0 for each Grade of toxicity except the term “creatinine clearance decreased” which is derived from the CTC term “renal/genitourinary-other”.

[c] According to NCI CTC Criteria version 2.0, this adverse event term should only be reported as Grade 1 or 2.

The following additional adverse reactions were observed in patients with malignant pleural mesothelioma randomly assigned to receive ALIMTA plus cisplatin.

Incidence 1% to 5%

Body as a Whole — febrile neutropenia, infection, pyrexia
Dermatology/Skin — urticaria
General Disorders — chest pain
Metabolism and Nutrition — increased AST, increased ALT, increased GGT
Renal — renal failure

Incidence Less than 1%

Cardiovascular — arrhythmia
Neurology — motor neuropathy

Effects of Vitamin Supplementations on Toxicity

Table 9 compares the incidence (percentage of patients) of CTC Grade 3/4 toxicities in patients who received vitamin supplementation with daily folic acid and vitamin B_{12} from the time of enrollment in the study (fully supplemented) with the

incidence in patients who never received vitamin supplementation (never supplemented) during the study in the ALIMTA plus cisplatin arm.

Table 9: Selected Grade 3/4 Adverse Events Comparing Fully Supplemented versus Never Supplemented Patients in the ALIMTA plus Cisplatin arm (% incidence)

Adverse Event[a] (%)	**Fully Supplemented Patients** (N=168)	**Never Supplemented Patients** (N=32)
Neutropenia/granulocytopenia	23	38
Thrombocytopenia	5	9
Vomiting	11	31
Febrile neutropenia	1	9
Infection with Grade 3/4 neutropenia	0	6
Diarrhea	4	9

[a] Refer to NCI CTC criteria for lab and non-laboratory values for each grade of toxicity (Version 2.0).

The following adverse events were greater in the fully supplemented group compared to the never supplemented group: hypertension (11%, 3%), chest pain (8%, 6%), and thrombosis/embolism (6%, 3%).

No relevant effect for ALIMTA safety due to gender or race was identified, except an increased incidence of rash in men (24%) compared to women (16%).

Additional Experience Across Clinical Trials

Sepsis, which in some cases was fatal, occurred in approximately 1% of patients.

Esophagitis occurred in less than 1% of patients.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ALIMTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

These reactions occurred with ALIMTA when used as a single-agent and in combination therapies.

Gastrointestinal — colitis, pancreatitis

General Disorders and Administration Site Conditions — edema

Injury, poisoning, and procedural complications — Radiation recall has been reported in patients who have previously received radiotherapy.

Respiratory — interstitial pneumonitis

Skin — Bullous conditions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Some cases were fatal.

7 DRUG INTERACTIONS

7.1 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Although ibuprofen (400 mg four times a day) can decrease the clearance of pemetrexed, it can be administered with ALIMTA in patients with normal renal function (creatinine clearance ≥80 mL/min). No dose adjustment of ALIMTA is needed with concomitant NSAIDs in patients with normal renal function *[see Clinical Pharmacology (12.3)]*.

Caution should be used when administering NSAIDs concurrently with ALIMTA to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min).

NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided 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 (e.g., meloxicam, nabumetone), patients 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, renal, and gastrointestinal toxicity.

7.2 Nephrotoxic Drugs

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects - Pregnancy Category D *[see Warnings and Precautions (5.6)]*

Based on its mechanism of action, ALIMTA can cause fetal harm when administered to a pregnant woman. There are no adequate and well controlled studies of ALIMTA in pregnant women. Pemetrexed was embryotoxic, fetotoxic, and teratogenic in mice. In mice, repeated intraperitoneal doses of pemetrexed when given during organogenesis caused fetal malformations (incomplete ossification of talus and skull bone; about 1/833rd the recommended intravenous human dose on a mg/m^2 basis), and cleft palate (1/33rd the recommended intravenous human dose on a mg/m^2 basis). Embryotoxicity was characterized by increased embryo-fetal

deaths and reduced litter sizes. If ALIMTA is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use effective contraceptive measures to prevent pregnancy during the treatment with ALIMTA.

8.3 Nursing Mothers

It is not known whether ALIMTA or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ALIMTA, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug for the mother.

8.4 Pediatric Use

Efficacy of ALIMTA in pediatric patients has not been demonstrated. ALIMTA was administered as an intravenous infusion over 10 minutes on Day 1 of a 21 day cycle to pediatric patients with recurrent solid tumors in a Phase 1 study (32 patients) and a Phase 2 study (72 patients). All patients received pretreatment with vitamin B_{12} and folic acid supplementation and dexamethasone. The dose escalation in the Phase 1 study determined the maximum tolerated dose was 1910 mg/m^2 and this dose (or 60 mg/kg for patients <12 months old) was evaluated in the Phase 2 study of patients with relapsed or refractory osteosarcoma, Ewing sarcoma/peripheral PNET, rhabdomyosarcoma, neuroblastoma, ependymoma, medulloblastoma/supratentorial PNET, or non-brainstem high grade glioma. No responses were observed among the 72 patients in this Phase 2 trial. The most common toxicities reported were hematological (leukopenia, neutropenia/granulocytopenia, anemia, thrombocytopenia, and lymphopenia), liver function abnormalities (increased ALT/AST), fatigue, and nausea.

The single dose pharmacokinetics of ALIMTA administered in doses ranging from 400 to 2480 mg/m^2 were evaluated in the Phase 1 trial in 22 patients (13 males and 9 females) aged 4 to 18 years (average age 12 years). Pemetrexed exposure (AUC and C_{max}) appeared to increase proportionally with dose. The average pemetrexed clearance (2.30 L/h/m^2) and half-life (2.3 hours) in pediatric patients were comparable to values reported in adults.

8.5 Geriatric Use

ALIMTA is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Renal function monitoring is recommended with administration of ALIMTA. No dose reductions other than those recommended for all patients are necessary for patients 65 years of age or older *[see Dosage and Administration (2.4)]*.

Of 3,946 patients (34.0% ≥65) studied across the five clinical trials *[see Clinical Studies (14.1, 14.2, 14.3, and 14.4)]*, the effect of ALIMTA on survival was similar in patients <65 compared to ≥65 years of age. There were no differences in safety with the exception of the following Grade 3-4 adverse reactions, which were noted in at least one of the five trials to be greater in patients 65 years of age and older as compared to younger patients: anemia, fatigue, thrombocytopenia, hypertension, and neutropenia.

8.6 Patients with Hepatic Impairment

There was no effect of elevated AST, ALT, or total bilirubin on the pharmacokinetics of pemetrexed. However, no formal studies have been conducted to examine the pharmacokinetics of pemetrexed in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Patients with Renal Impairment

ALIMTA is known to be primarily excreted by the kidneys. Decreased renal function will result in reduced clearance and greater exposure (AUC) to ALIMTA compared with patients with normal renal function *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*. Cisplatin coadministration with ALIMTA has not been studied in patients with moderate renal impairment.

8.8 Gender

Of 3,946 patients (Male 70.5%) studied across the five registration studies for ALIMTA indications *[see Clinical Studies (14.1, 14.2, 14.3, and 14.4)]*, the effect of ALIMTA on survival was similar in female and male patients.

8.9 Race

Of 3,946 patients (Caucasian 78.6%) studied across the five registration studies for ALIMTA indications *[see Clinical Studies (14.1, 14.2, 14.3, and 14.4)]*, the effect of ALIMTA on survival was similar in the Caucasian and non-Caucasian patients.

10 OVERDOSAGE

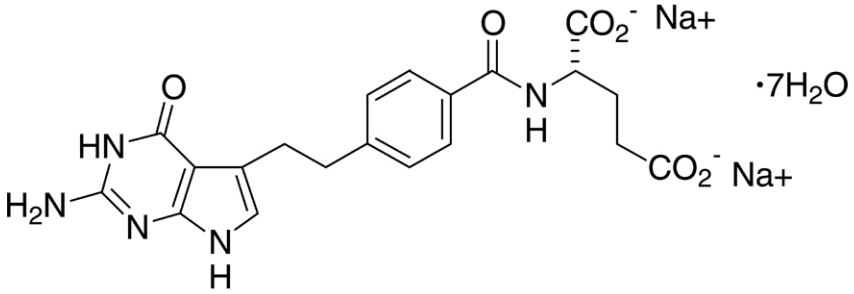
There have been few cases of ALIMTA overdose. Reported toxicities included neutropenia, anemia, thrombocytopenia, mucositis, and rash. Anticipated complications of overdose include bone marrow suppression as manifested by neutropenia, thrombocytopenia, and anemia. In addition, infection with or without fever, diarrhea, and mucositis may be seen. If an overdose occurs, general supportive measures should be instituted as deemed necessary by the treating physician.

In clinical trials, leucovorin was permitted for CTC Grade 4 leukopenia lasting ≥3 days, CTC Grade 4 neutropenia lasting ≥3 days, and immediately for CTC Grade 4 thrombocytopenia, bleeding associated with Grade 3 thrombocytopenia, or Grade 3 or 4 mucositis. The following intravenous doses and schedules of leucovorin were recommended for intravenous use: 100 mg/m^2, intravenously once, followed by leucovorin, 50 mg/m^2, intravenously every 6 hours for 8 days.

The ability of ALIMTA to be dialyzed is unknown.

11 DESCRIPTION

Pemetrexed disodium heptahydrate 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 is a white to almost-white solid with a molecular formula of $C_{20}H_{19}N_5Na_2O_6 \bullet 7H_2O$ and a molecular weight of 597.49. The structural formula is as follows:



ALIMTA is supplied as a sterile lyophilized powder for intravenous infusion available in single-dose vials. The product is a white to either light yellow or green-yellow lyophilized solid. Each 100-mg or 500-mg vial of ALIMTA contains pemetrexed disodium equivalent to 100 mg pemetrexed and 106 mg mannitol or 500 mg pemetrexed and 500 mg mannitol, respectively. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ALIMTA, pemetrexed for injection, is a folate analog metabolic inhibitor that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication. In vitro studies have shown that pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is taken into cells by membrane carriers such as the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are inhibitors of TS and GARFT. Polyglutamation is a time- and concentration-dependent process that occurs in tumor cells and, is thought to occur to a lesser extent, in normal tissues. Polyglutamated metabolites are thought to have an increased intracellular half-life resulting in prolonged drug action in malignant cells.

12.2 Pharmacodynamics

Preclinical studies have shown that pemetrexed inhibits the in vitro growth of mesothelioma cell lines (MSTO-211H, NCI-H2052). Studies with the MSTO-211H mesothelioma cell line showed synergistic effects when pemetrexed was combined concurrently with cisplatin.

Absolute neutrophil counts (ANC) following single-agent administration of ALIMTA to patients not receiving folic acid and vitamin B_{12} supplementation were characterized using population pharmacodynamic analyses. Severity of hematologic toxicity, as measured by the depth of the ANC nadir, correlates with the systemic exposure, or area under the curve (AUC) of pemetrexed. It was also observed that lower ANC nadirs occurred in patients with elevated baseline cystathionine or homocysteine concentrations. The levels of these substances can be reduced by folic acid and vitamin B_{12} supplementation. There is no cumulative effect of pemetrexed exposure on ANC nadir over multiple treatment cycles.

Time to ANC nadir with pemetrexed systemic exposure (AUC), varied between 8 to 9.6 days over a range of exposures from 38.3 to 316.8 mcg•hr/mL. Return to baseline ANC occurred 4.2 to 7.5 days after the nadir over the same range of exposures.

12.3 Pharmacokinetics

Absorption

The pharmacokinetics of ALIMTA administered as a single-agent in doses ranging from 0.2 to 838 mg/m^2 infused over a 10-minute period have been evaluated in 426 cancer patients with a variety of solid tumors. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration (C_{max}) increase proportionally with dose. The pharmacokinetics of pemetrexed do not change over multiple treatment cycles.

Distribution

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

Metabolism and Excretion

Pemetrexed is not metabolized to an appreciable extent and is primarily eliminated in the urine, with 70% to 90% of the dose recovered unchanged within the first 24 hours following administration. The clearance decreases, and exposure (AUC) increases, as renal function decreases. The total systemic clearance of pemetrexed is 91.8 mL/min and the elimination half-life of pemetrexed is 3.5 hours in patients with normal renal function (creatinine clearance of 90 mL/min).

The pharmacokinetics of pemetrexed in special populations were examined in about 400 patients in controlled and single arm studies.

In vitro studies indicate that pemetrexed is a substrate of OAT3 (organic anion transporter 3), a transporter that may play a role in active secretion of pemetrexed.

Effect of Age, Gender or Race

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

The pharmacokinetics of pemetrexed were not different in male and female patients.

The pharmacokinetics of pemetrexed were similar in Caucasians and patients of African descent. Insufficient data are available to compare pharmacokinetics for other ethnic groups.

Effect of Hepatic Insufficiency

There was no effect of elevated AST, ALT, or total bilirubin on the pharmacokinetics of pemetrexed. However, studies of hepatically impaired patients have not been conducted *[see Dosage and Administration (2.4) and Use in Specific Populations (8.6)]*.

Effect of Renal Insufficiency

Pharmacokinetic analyses of pemetrexed included 127 patients with reduced renal function. Plasma clearance of pemetrexed decreases as renal function decreases, with a resultant increase in systemic exposure. Patients with creatinine clearances of 45, 50, and 80 mL/min had 65%, 54%, and 13% increases, respectively in pemetrexed total systemic exposure (AUC) compared to patients with creatinine clearance of 100 mL/min *[see Warnings and Precautions (5.4) and Dosage and Administration (2.4)]*.

Effect of Third Space Fluid

The effect of third space fluid, such as pleural effusion and ascites, on ALIMTA is not fully defined. A study of ALIMTA 500 mg/m^2 was performed in 31 solid tumor patients with stable third space fluid (All but 2 of the 31 patients included in study had mild or moderate amounts of third space fluid). Moderate pleural effusion was defined in the study as less than 1/3 the way up on one side with obscuring of the entire hemidiaphragm. Moderate ascites was defined as that detectable on physical exam. The pemetrexed plasma concentrations in these patients were comparable to those observed in previous clinical trials in patients without third space fluid collections. Thus, drainage of mild or moderate third space fluid collection prior to ALIMTA treatment should be considered, but is probably not necessary. The effect of severe third space fluid on pharmacokinetics is not known.

Effect of Ibuprofen

Ibuprofen doses of 400 mg four times a day reduce pemetrexed's clearance by about 20% (and increase AUC by 20%) in patients with normal renal function. The effect of greater doses of ibuprofen on pemetrexed pharmacokinetics is unknown *[see Drug Interactions (7.1)]*.

Effect of Aspirin

Aspirin, administered in low to moderate doses (325 mg every 6 hours), does not affect the pharmacokinetics of pemetrexed. The effect of greater doses of aspirin on pemetrexed pharmacokinetics is unknown.

Effect of Cisplatin

Cisplatin does not affect the pharmacokinetics of pemetrexed and the pharmacokinetics of total platinum are unaltered by pemetrexed.

Effect of Vitamins

Coadministration of oral folic acid or intramuscular vitamin B_{12} does not affect the pharmacokinetics of pemetrexed.

Drugs Metabolized by Cytochrome P450 Enzymes

Results from in vitro studies with human liver microsomes predict that pemetrexed would not cause clinically significant inhibition of metabolic clearance of drugs metabolized by CYP3A, CYP2D6, CYP2C9, and CYP1A2.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies have been conducted with pemetrexed. Pemetrexed was clastogenic in the in vivo micronucleus assay in mouse bone marrow but was not mutagenic in multiple in vitro tests (Ames assay, CHO cell assay). Pemetrexed administered at i.v. doses of 0.1 mg/kg/day or greater to male mice (about 1/1666 the recommended human dose on a mg/m^2 basis) resulted in reduced fertility, hypospermia, and testicular atrophy.

14 CLINICAL STUDIES

14.1 Non-Small Cell Lung Cancer (NSCLC) - Combination with Cisplatin

A multi-center, randomized, open-label study in 1725 chemonaive patients with Stage IIIb/IV NSCLC was conducted to compare the overall survival following treatment with ALIMTA in combination with cisplatin (AC) versus gemcitabine in combination with cisplatin (GC). ALIMTA was administered intravenously over 10 minutes at a dose of 500 mg/m^2 with cisplatin administered intravenously at a dose of 75 mg/m^2 after ALIMTA administration, on Day 1 of each 21-day cycle. Gemcitabine was administered at a dose of 1250 mg/m^2 on Day 1 and Day 8, and cisplatin was administered intravenously at a dose of 75 mg/m^2 after administration of gemcitabine, on Day 1 of each 21-day cycle. Treatment was administered up to a total of 6 cycles, and patients in both treatment arms received folic acid, vitamin B_{12}, and dexamethasone *[see Dosage and Administration (2.3)]*.

Patient demographics of the intent to treat (ITT) population are shown in Table 10. The demographics and disease characteristics were well balanced.

Table 10: First-Line Therapy: Summary of Patient Characteristics in Study of NSCLC

Patient characteristic	**ALIMTA plus Cisplatin (AC) (N=862)**	**Gemcitabine plus Cisplatin (GC) (N=863)**
Age (yrs)		
Median (range)	61.1 (28.8-83.2)	61.0 (26.4-79.4)
Gender		
Male/Female	70.2%/29.8%	70.1%/29.9%

Origin		
Caucasian	669 (77.6%)	680 (78.8%)
Hispanic	27 (3.1%)	23 (2.7%)
Asian	146 (16.9%)	141 (16.3%)
African descent	18 (2.1%)	18 (2.1%)
Stage at Entry		
IIIb/IV	23.8%/76.2%	24.3%/75.7%
Histology		
Nonsquamous NSCLC[a]	618 (71.7%)	634 (73.5%)
Adenocarcinoma	436 (50.6%)	411 (47.6%)
Large cell	76 (8.8%)	77 (8.9%)
Other[b]	106 (12.3%)	146 (16.9%)
Squamous	244 (28.3%)	229 (26.5%)
ECOG PS[c,d]		
0/1	35.4%/64.6%	35.6%/64.3%
Smoking History[e]		
Ever/never smoker	83.1%/16.9%	83.9%/16.1%

[a] Includes adenocarcinoma, large cell, and other histologies except those with squamous cell type.

[b] The subgroup of "other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma.

[c] Eastern Cooperative Oncology Group Performance Status.

[d] ECOG PS was not reported for all randomized patients. Percentages are representative of N=861 for the ALIMTA plus cisplatin arm, and N=861 for the gemcitabine plus cisplatin arm.

[e] Smoking history was collected for 88% of randomized patients (N=757 for the ALIMTA plus cisplatin arm and N=759 for the gemcitabine plus cisplatin arm).

Patients received a median of 5 cycles of treatment in both study arms. Patients treated with ALIMTA plus cisplatin received a relative dose intensity of 94.8% of the protocol-specified ALIMTA dose intensity and 95.0% of the protocol-specified cisplatin dose intensity. Patients treated with gemcitabine plus cisplatin received a relative dose intensity of 85.8% of the protocol-specified gemcitabine dose intensity and 93.5% of the protocol-specified cisplatin dose intensity.

The primary endpoint in this study was overall survival. The median survival time was 10.3 months in the ALIMTA plus cisplatin treatment arm and 10.3 months in the gemcitabine plus cisplatin arm, with an adjusted hazard ratio of 0.94.

Table 11: First-Line Therapy: Efficacy in NSCLC - ITT Population

	ALIMTA plus Cisplatin (N=862)	**Gemcitabine plus 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)[a,b] (95% CI)	0.94 (0.84-1.05)	
Median progression-free survival (95% CI)	4.8 mos (4.6-5.3)	5.1 mos (4.6-5.5)
Adjusted hazard ratio (HR)[a,b] (95% CI)	1.04 (0.94-1.15)	
Overall response rate (95% CI)	27.1% (24.2-30.1)	24.7% (21.8-27.6)

[a] Adjusted for gender, stage, basis of diagnosis, and performance status.

[b] A HR that is less than 1.0 indicates that survival is better in the AC arm than in the GC arm. Alternatively, a HR that is greater than 1.0 indicates survival is better in the GC arm than in the AC arm.

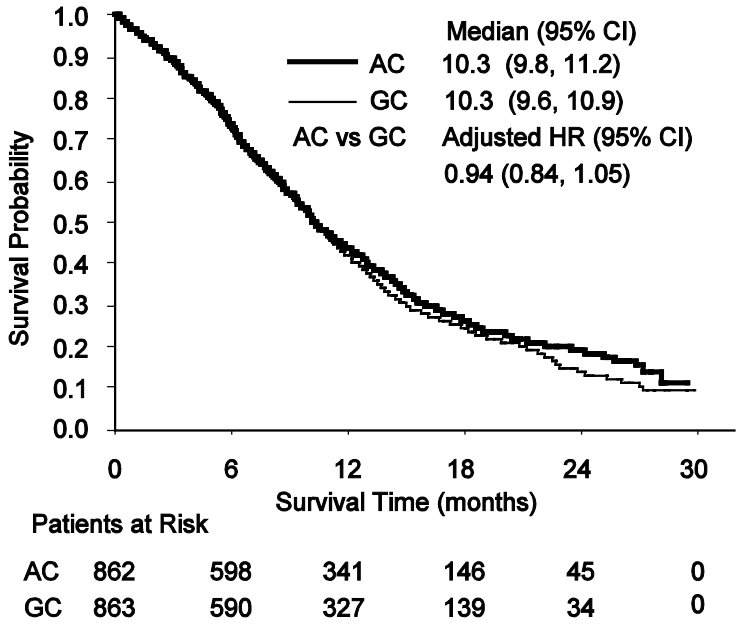


Figure 1: Kaplan-Meier Curves for Overall Survival ALIMTA plus Cisplatin (AC) versus Gemcitabine plus Cisplatin (GC) in NSCLC - ITT Population.

A pre-specified analysis of the impact of NSCLC histology on overall survival was examined. Clinically relevant differences in survival according to histology were observed and are shown in Table 12. This difference in treatment effect for ALIMTA based on histology demonstrating a lack of efficacy in squamous cell histology was also observed in the single-agent, second-line study and the maintenance study *[see Clinical Studies (14.2, 14.3)]*.

Table 12: First-Line Therapy: Overall Survival in NSCLC Histologic Subgroups

Histology Subgroup	**Median Overall Survival in Months (95% CI)**				**Unadjusted Hazard Ratio (HR)[a,b] (95% CI)**	**Adjusted Hazard Ratio (HR)[a,b,c] (95% CI)**
	ALIMTA plus Cisplatin		Gemcitabine plus Cisplatin			
Nonsquamous NSCLC[d] (N=1252)	11.0 (10.1-12.5)	N=618	10.1 (9.3-10.9)	N=634	0.84 (0.74-0.96)	0.84 (0.74-0.96)
Adenocarcinoma (N=847)	12.6 (10.7-13.6)	N=436	10.9 (10.2-11.9)	N=411	0.84 (0.71-0.98)	0.84 (0.71-0.99)
Large Cell (N=153)	10.4 (8.6-14.1)	N=76	6.7 (5.5-9.0)	N=77	0.68 (0.48-0.97)	0.67 (0.48-0.96)
Other[e] (N=252)	8.6 (6.8-10.2)	N=106	9.2 (8.1-10.6)	N=146	1.12 (0.84-1.49)	1.08 (0.81-1.45)
Squamous Cell (N=473)	9.4 (8.4-10.2)	N=244	10.8 (9.5-12.1)	N=229	1.22 (0.99-1.50)	1.23 (1.00-1.51)

[a] A HR that is less than 1.0 indicates that survival is better in the AC arm than in the GC arm. Alternatively, a HR that is greater than 1.0 indicates survival is better in the GC arm than in the AC arm.

[b] Unadjusted for multiple comparisons.

[c] HRs adjusted for ECOG PS, gender, disease stage, and basis for pathological diagnosis (histopathological/cytopathological).

[d] Includes adenocarcinoma, large cell, and other histologies except those with squamous cell type.

[e] The subgroup of “other” represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma.

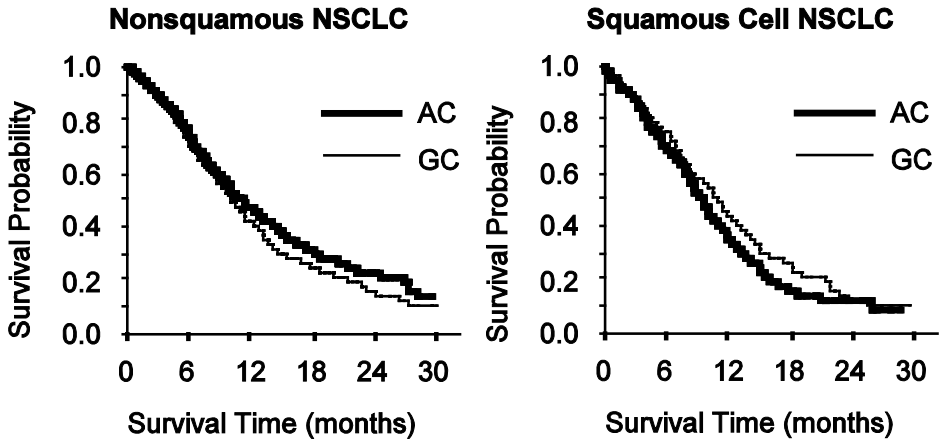


Figure 2: Kaplan-Meier Curves for Overall Survival ALIMTA plus Cisplatin (AC) versus Gemcitabine plus Cisplatin (GC) in NSCLC - Nonsquamous NSCLC and Squamous Cell NSCLC.

14.2 Non-Small Cell Lung Cancer - Maintenance

ALIMTA Maintenance Following Non-ALIMTA Containing Platinum-Based, Induction Therapy

A multi-center, randomized, double-blind, placebo-controlled study was conducted in 663 patients with Stage IIIb/IV NSCLC who did not progress after four cycles of platinum-based chemotherapy. Patients who did not progress were randomized 2:1 to receive ALIMTA or placebo immediately following platinum-based chemotherapy. Of the randomized patients, 47.2% versus 52.7% achieved a complete or partial response to induction therapy and 51.9% versus 47.3% had stable disease after induction therapy in the ALIMTA and placebo arms, respectively. ALIMTA was administered intravenously over 10 minutes at a dose of 500 mg/m^2 on Day 1 of each 21-day cycle, until disease progression. Patients in both study arms received folic acid, vitamin B_{12}, and dexamethasone *[see Dosage and Administration (2.3)]*.

The study was designed to demonstrate superior progression-free survival and overall survival of ALIMTA over placebo. Progression-free survival (PFS) was assessed by independent review. Patient characteristics of the intent to treat (ITT) population are shown in Table 13. The demographics and baseline disease characteristics were well balanced between study arms.

Table 13: Maintenance Therapy Following Platinum-Based Induction Therapy: Summary of Patient Characteristics in Study of NSCLC

Patient characteristic	**ALIMTA (N=441)**	**Placebo (N=222)**
Age (yrs)		
Median (range)	60.6 (25.6-82.6)	60.4 (35.4-78.5)
Gender		
Male/Female	73.0%/27.0%	72.5%/27.5%
Ethnic Origin		
Caucasian	279 (63.3%)	149 (67.1%)
East Asian	104 (23.6%)	50 (22.5%)
Other	58 (13.2%)	23 (10.4%)
Stage at Entry[a]		
IIIb/IV	18.0%/82.0%	21.2%/78.8%
Histology (%)		
Nonsquamous NSCLC[b]	325 (73.7%)	156 (70.3%)
Adenocarcinoma	222 (50.3%)	106 (47.7%)
Large cell	10 (2.3%)	10 (4.5%)
Other[c]	93 (21.1%)	40 (18.0%)
Squamous	116 (26.3%)	66 (29.7%)
ECOG PS[d]		
0/1	40.1%/59.9%	38.3%/61.7%
Smoking History[e]		
Ever/never smoker	74.1%/25.9%	71.5%/28.5%
Time from start of induction therapy to study randomization (months)		
Median (range)	3.25 (1.6-4.8)	3.29 (2.7-5.1)

[a] Stage at Entry was not reported for all randomized patients. Percentages are representative of N=440 for the ALIMTA arm and N=222 for the placebo arm.

[b] Includes patients with adenocarcinoma, large cell, and other histologic diagnoses.

[c] The subgroup of "Other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, large cell carcinoma, or squamous cell carcinoma.

[d] Eastern Cooperative Oncology Group Performance Status (ECOG PS) was not reported for all randomized patients. Percentages are representative of N=439 for the ALIMTA arm, and N=222 for the placebo arm.

[e] Smoking history was not reported for all randomized patients. Percentages are representative of N=437 for the ALIMTA arm and N=221 for the placebo arm.

Patients received a median of 5 cycles of ALIMTA and 3.5 cycles of placebo. Patients randomized to ALIMTA received a relative dose intensity of 95.7%. A total of 213 patients (48.3%) completed ≥6 cycles and a total of 98 patients (22.6%) 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). A difference in treatment outcomes was observed according to histologic classification. For the population of patients with nonsquamous NSCLC, 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)). For the population of patients with squamous NSCLC, ALIMTA did not improve OS compared to placebo (median 9.9 months versus 10.8 months, HR=1.07 (95% CI: 0.77-1.50)) or PFS (median 2.4 months versus 2.5 months, HR=1.03 (95% CI: 0.71-1.49)). This difference in treatment effect for ALIMTA based on histology demonstrating lack of benefit in squamous cell histology was also observed in the first-line and second-line studies. *[see Clinical Studies (14.1, 14.3)]*

Efficacy results for the overall patient population are presented in Table 14 and Figure 3, and efficacy results by pre-specified histologic subgroups are presented in Table 15 and Figure 4, below.

Table 14: Maintenance Therapy Following Platinum-Based Induction Therapy: Efficacy of ALIMTA versus Placebo in NSCLC - ITT Population

Efficacy Parameter[a,b]	**ALIMTA (N=441)**	**Placebo (N=222)**
Median overall survival[c] (95% CI)	13.4 mos (11.9-15.9)	10.6 mos (8.7-12.0)
Hazard ratio (HR)[c] (95% CI)	0.79 (0.65-0.95)	
p-value	p=0.012	
Median progression-free survival (95% CI)	4.0 mos (3.1-4.4)	2.0 mos (1.5-2.8)
Hazard ratio (HR)[c] (95% CI)	0.60 (0.49-0.73)	
p-value	p<0.00001	

[a] PFS and OS were calculated from time of randomization, after completion of 4 cycles of induction platinum-based chemotherapy.

[b] Values for PFS given based on independent review (ALIMTA N=387, Placebo N=194).

[c] Unadjusted hazard ratios are provided. A HR <1.0 indicates that the result is better in the ALIMTA arm than in the placebo arm.

Table 15: Maintenance Therapy Following Platinum-Based Induction Therapy: Efficacy in NSCLC by Histologic Subgroups[a]

	Overall Survival		**Progression-Free Survival[b]**	
	ALIMTA	**Placebo**	**ALIMTA**	**Placebo**
	Median (months)	**Median (months)**	**Median (months)**	**Median (months)**
	HR[c] (95% CI)		**HR[c] (95% CI)**	
Nonsquamous NSCLC[d]	**15.5**	**10.3**	**4.4**	**1.8**
N=481	**0.70 (0.56-0.88)**		**0.47 (0.37-0.60)**	
Adenocarcinoma	16.8	11.5	4.6	2.7
N=328	0.73 (0.56-0.96)		0.51 (0.38-0.68)	
Large cell carcinoma	8.4	7.9	4.5	1.5
N=20	0.98 (0.36-2.65)		0.40 (0.12-1.29)	
Other[e]	11.3	7.7	4.1	1.6
N=133	0.61 (0.40-0.94)		0.44 (0.28-0.68)	
Squamous cell	**9.9**	**10.8**	**2.4**	**2.5**
N=182	**1.07 (0.77-1.50)**		**1.03 (0.71-1.49)**	

[a] PFS and OS were calculated from time of randomization, after completion of 4 cycles of induction platinum-based chemotherapy. All results unadjusted for multiple comparisons.

[b] Values for PFS are given based on independent review (ALIMTA N=387, Placebo N=194).

[c] Unadjusted hazard ratios are provided. A HR <1.0 indicates that the result is better in the ALIMTA arm than in the placebo arm. A HR >1.0 indicates that the result is better in the placebo arm than in the ALIMTA arm.

[d] Includes patients with adenocarcinoma, large cell carcinoma, and other histology.

[e] The subgroup of "Other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, large cell carcinoma, or squamous cell carcinoma.

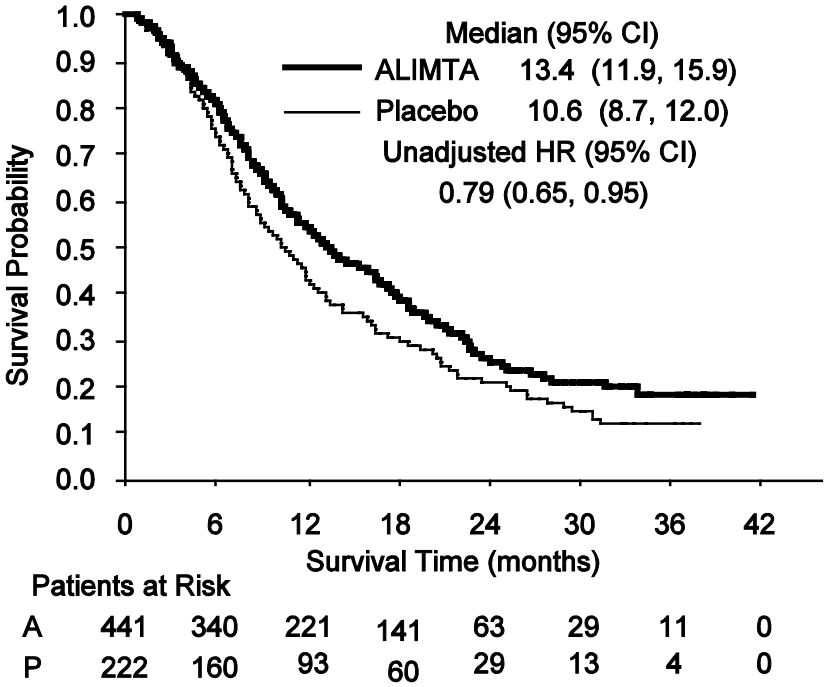


Figure 3: Kaplan-Meier Curve for Overall Survival ALIMTA (A) versus Placebo (P) in NSCLC - ITT Population.

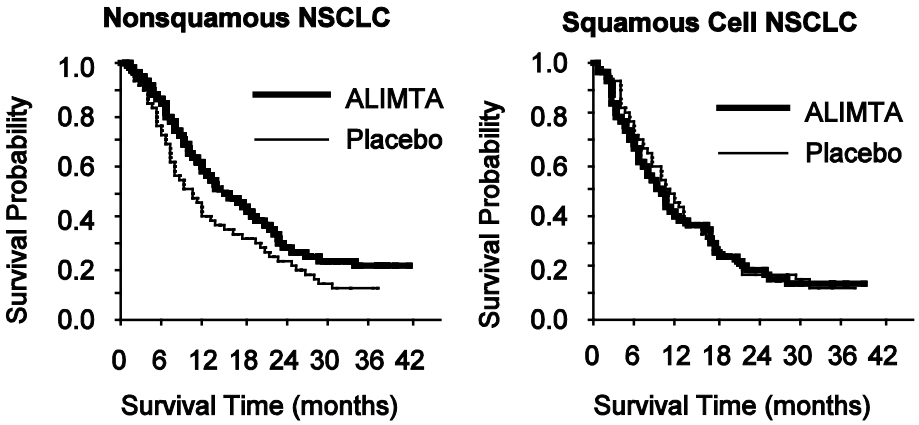


Figure 4: Kaplan-Meier Curves for Overall Survival ALIMTA versus Placebo in NSCLC - Nonsquamous NSCLC and Squamous Cell NSCLC.

Continuation of ALIMTA as Maintenance Following ALIMTA Plus Platinum Induction Therapy

A multi-center, randomized, double-blind, placebo-controlled study was conducted to evaluate continuation of ALIMTA in patients with Stage IIIb/IV nonsquamous NSCLC. Patients completing induction treatment of four cycles of ALIMTA plus cisplatin with stable disease or better and PS 0/1 were randomized (2:1) to maintenance treatment with ALIMTA or placebo. Randomization was stratified by response to induction (complete response (CR)/partial response (PR) versus stable disease (SD)), disease stage (IIIb versus IV), and ECOG performance status (0 versus 1). ALIMTA was administered intravenously over 10 minutes at a dose of 500 mg/m^2 on Day 1 of each 21-day cycle and continued until disease progression. Patients in both study arms received folic acid, vitamin B_{12}, and dexamethasone *[see Dosage and Administration (2.3)]*. The main efficacy outcome was investigator-assessed progression-free survival.

A total of 539 patients were randomized; all completed four cycles of ALIMTA and cisplatin induction prior to randomization. Of the randomized patients, 44% versus 42% achieved a complete or partial response to induction therapy and 53% versus 53% had stable disease after induction treatment in the ALIMTA or the placebo arms respectively.

Patient demographics of the intent to treat (ITT) population are shown in Table 16.

Table 16: ALIMTA as Maintenance Therapy Following ALIMTA Plus Cisplatin Induction Therapy: Summary of Patient Characteristics in Study of Nonsquamous NSCLC

Patient characteristic	**ALIMTA (N=359)**	**Placebo (N=180)**
Age (yrs)		
Median	61.0	62.4
Range	31.9-78.7	34.9-83.3
Gender (%)		
Male	201 (56%)	112 (62%)
Female	158 (44%)	68 (38%)
Ethnic Origin (%)		
Caucasian	339 (94%)	171 (95%)
Asian	16 (4.5%)	8 (4.4%)
African	4 (1.1%)	1 (0.6%)
Stage at Entry		
IIIb	31 (9%)	18 (10%)
IV	328 (91%)	162 (90%)
Histology (%)		
Nonsquamous NSCLC[a]		
Adenocarcinoma	310 (86%)	161 (89%)
Large cell	24 (7%)	12 (7%)
Other[b]	25 (7%)	7 (3.9%)
ECOG PS (%)		
0	113 (32%)	60 (33%)
1	245 (68%)	118 (66%)
Smoking History[c]		
Ever	274 (76%)	144 (80%)
Never smoker	83 (23%)	34 (19%)

[a] Histological or cytological diagnosis of NSCLC defined as other than predominantly squamous cell histology (squamous cell and/or mixed small cell, non-small cell histology were not permitted on this study).

[b] The subcategory of "Other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma or large-cell carcinoma.

[c] Smoking history was not reported for all randomized patients.

Patients received a median of four cycles of ALIMTA maintenance or placebo. The percentages of patients that received post-study treatment were similar (64% in the ALIMTA arm and 72% in the placebo arm).

The trial showed a statistically significant improvement in progression-free survival and in overall survival for patients randomized to ALIMTA maintenance. Efficacy results are presented in Table 17 and Figure 5.

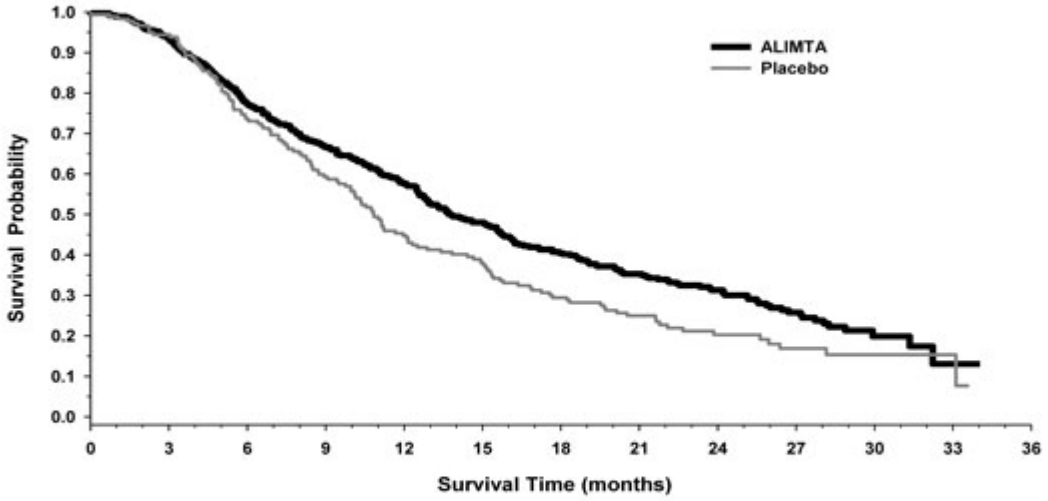
Table 17: ALIMTA Maintenance Therapy Following ALIMTA Plus Cisplatin Induction Therapy: Efficacy of ALIMTA versus Placebo in Nonsquamous NSCLC

Efficacy Parameter[a,b]	**ALIMTA (N=359)**	**Placebo (N=180)**
Median overall survival[c] (95% CI)	13.9 mos (12.8-16.0)	11.0 mos (10.0-12.5)
Hazard ratio (HR)[c] (95% CI)	0.78 (0.64-0.96)	
p-value	p=0.02	
Median progression-free survival (95% CI)	4.1 mos (3.2-4.6)	2.8 mos (2.6-3.1)
Hazard ratio (HR)[c] (95% CI)	0.62 (0.49-0.79)	
p-value	p<0.0001	

[a] PFS and OS were calculated from time of randomization, after completion of 4 cycles of ALIMTA plus cisplatin induction therapy.

[b] Values for PFS given based on investigator assessment.

[c] A hazard ratio of less than 1 indicates that the maintenance treatment with pemetrexed is associated with lower risk of progression or death compared to treatment with placebo.



Patients at Risk

A	359	333	272	235	200	166	138	105	79	43	15	2	0
P	180	169	131	103	78	65	49	35	23	12	8	3	0

Figure 5: Kaplan-Meier Curves for Overall Survival ALIMTA versus Placebo in Nonsquamous NSCLC Following ALIMTA Plus Cisplatin Induction Therapy.

14.3 Non-Small Cell Lung Cancer - After Prior Chemotherapy

A multi-center, randomized, open label study was conducted in patients with Stage III or IV NSCLC after prior chemotherapy to compare the overall survival following treatment with ALIMTA versus docetaxel. ALIMTA was administered intravenously over 10 minutes at a dose of 500 mg/m^2 and docetaxel was administered at 75 mg/m^2 as a 1-hour intravenous infusion. Both drugs were given on Day 1 of each 21-day cycle. All patients treated with ALIMTA received vitamin supplementation with folic acid and vitamin B_{12}. The study was intended to show either an overall survival superiority or non-inferiority of ALIMTA to docetaxel. Patient demographics of the intent to treat (ITT) population are shown in Table 18.

Table 18: Second-Line Therapy: Summary of Patient Characteristics in NSCLC Study

Patient characteristic	**ALIMTA** (N=283)	**Docetaxel** (N=288)
Age (yrs)		
Median (range)	59 (22-81)	57 (28-87)
Gender (%)		
Male/Female	68.6/31.4	75.3/24.7
Stage at Entry (%)		
III/IV	25.1/74.9	25.3/74.7
Diagnosis/Histology (%)		
Adenocarcinoma	154 (54.4)	142 (49.3)
Squamous	78 (27.6)	94 (32.6)
Bronchoalveolar	4 (1.4)	1 (0.3)
Other	47 (16.6)	51 (17.7)
Performance Status (%)[a]		
0-1	234 (88.6)	240 (87.6)
2	30 (11.4)	34 (12.4)

[a] Performance status was not reported for all randomized patients. Percentages are representative of N=264 for the ALIMTA arm and N=274 for the docetaxel arm.

The primary endpoint in this study was overall survival. The median survival time was 8.3 months in the ALIMTA treatment arm and 7.9 months in the docetaxel arm, with a hazard ratio of 0.99 (see Table 19). The study did not show an overall survival superiority of ALIMTA.

Table 19: Efficacy of ALIMTA versus Docetaxel in Non-Small Cell Lung Cancer - ITT Population

	ALIMTA (N=283)	Docetaxel (N=288)
Median overall survival (95% CI)	8.3 mos (7.0-9.4)	7.9 mos (6.3-9.2)
Hazard ratio (HR) (95% CI)	0.99 (0.82-1.20)	
Median progression-free survival (95% CI)	2.9 mos (2.4-3.1)	2.9 mos (2.7-3.4)
Hazard ratio (HR) (95% CI)	0.97 (0.82-1.16)	
Overall response rate (95% CI)	8.5% (5.2-11.7)	8.3% (5.1-11.5)

A retrospective analysis of the impact of NSCLC histology on overall survival was examined. Clinically relevant differences in survival according to histology were observed and are shown in Table 20. This difference in treatment effect for ALIMTA based on histology demonstrating a lack of efficacy in squamous cell histology was also observed in the first-line combination study and in the maintenance study *[see Clinical Studies (14.1, 14.2)]*.

Table 20: Second-Line Therapy: Overall Survival of ALIMTA versus Docetaxel in NSCLC by Histologic Subgroups

Histology Subgroup	**Median Overall Survival in Months (95% CI)**				**Unadjusted Hazard Ratio (HR)[a,b] (95% CI)**	**Adjusted Hazard Ratio (HR)[a,b,c] (95% CI)**
	ALIMTA		Docetaxel			
Nonsquamous NSCLC[d] (N=399)	9.3 (7.8-9.7)	N=205	8.0 (6.3-9.3)	N=194	0.89 (0.71-1.13)	0.78 (0.61-1.00)
Adenocarcinoma (N=301)	9.0 (7.6-9.6)	N=158	9.2 (7.5-11.3)	N=143	1.09 (0.83-1.44)	0.92 (0.69-1.22)
Large Cell (N=47)	12.8 (5.8-14.0)	N=18	4.5 (2.3-9.1)	N=29	0.38 (0.18-0.78)	0.27 (0.11-0.63)
Other[e] (N=51)	9.4 (6.0-10.1)	N=29	7.9 (4.0-8.9)	N=22	0.62 (0.32-1.23)	0.57 (0.27-1.20)
Squamous Cell (N=172)	6.2 (4.9-8.0)	N=78	7.4 (5.6-9.5)	N=94	1.32 (0.93-1.86)	1.56 (1.08-2.26)

[a] A HR that is less than 1.0 indicates that survival is better in the ALIMTA arm than in the docetaxel arm. Alternatively, a HR that is greater than 1.0 indicates survival is better in the docetaxel arm than in the ALIMTA arm.
[b] Unadjusted for multiple comparisons.
[c] HRs adjusted for ECOG PS, time since prior chemotherapy, disease stage, and gender.
[d] Includes adenocarcinoma, large cell, and other histologies except those with squamous cell type.
[e] The subgroup of "other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma.

14.4 Malignant Pleural Mesothelioma

A multi-center, randomized, single-blind study in 448 chemonaive patients with malignant pleural mesothelioma (MPM) compared survival in patients treated with ALIMTA in combination with cisplatin to survival in 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. After 117 patients were treated, white cell and GI toxicity led to a change in protocol whereby all patients were given folic acid and vitamin B_{12} supplementation.

The primary analysis of this study was performed on the population of all patients randomly assigned to treatment who received study drug (randomized and treated). An analysis was also performed on patients who received folic acid and vitamin B_{12} supplementation during the entire course of study therapy (fully supplemented), as supplementation is recommended *[see Dosage and Administration (2.3)]*. Results in all patients and those fully supplemented were similar. Patient demographics are shown in Table 21.

Table 21: Summary of Patient Characteristics in MPM Study

Patient characteristic	**Randomized and Treated Patients**		**Fully Supplemented Patients**	
	ALIMTA/cis (N=226)	Cisplatin (N=222)	ALIMTA/cis (N=168)	Cisplatin (N=163)
Age (yrs)				

Median (range)	61 (29-85)	60 (19-84)	60 (29-85)	60 (19-82)
Gender (%)				
Male	184 (81.4)	181 (81.5)	136 (81.0)	134 (82.2)
Female	42 (18.6)	41 (18.5)	32 (19.0)	29 (17.8)
Origin (%)				
Caucasian	204 (90.3)	206 (92.8)	150 (89.3)	153 (93.9)
Hispanic	11 (4.9)	12 (5.4)	10 (6.0)	7 (4.3)
Asian	10 (4.4)	4 (1.9)	7 (4.2)	3 (1.8)
African descent	1 (0.4)	0	1 (0.6)	0
Stage at Entry (%)				
I	16 (7.1)	14 (6.3)	15 (8.9)	12 (7.4)
II	35 (15.6)	33 (15.0)	27 (16.2)	27 (16.8)
III	73 (32.4)	68 (30.6)	51 (30.5)	49 (30.4)
IV	101 (44.9)	105 (47.2)	74 (44.3)	73 (45.3)
Unspecified	1 (0.4)	2 (0.9)	1 (0.6)	2 (1.2)
Diagnosis/Histology[a] (%)				
Epithelial	154 (68.1)	152 (68.5)	117 (69.6)	113 (69.3)
Mixed	37 (16.4)	36 (16.2)	25 (14.9)	25 (15.3)
Sarcomatoid	18 (8.0)	25 (11.3)	14 (8.3)	17 (10.4)
Other	17 (7.5)	9 (4.1)	12 (7.1)	8 (4.9)
Baseline KPS[b] (%)				
70-80	109 (48.2)	97 (43.7)	83 (49.4)	69 (42.3)
90-100	117 (51.8)	125 (56.3)	85 (50.6)	94 (57.7)

[a] Only 67% of the patients had the histologic diagnosis of malignant mesothelioma confirmed by independent review.
[b] Karnofsky Performance Scale.

Table 22 and Figure 6 summarize the survival results for all randomized and treated patients regardless of vitamin supplementation status and those patients receiving vitamin supplementation from the time of enrollment in the trial.

Table 22: Efficacy of ALIMTA plus Cisplatin versus Cisplatin in Malignant Pleural Mesothelioma

Efficacy Parameter	**Randomized 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[a]	0.020		0.051	

[a] p-value refers to comparison between arms.

Similar results were seen in the analysis of patients (N=303) with confirmed histologic diagnosis of malignant pleural mesothelioma. There were too few non-white patients to assess possible ethnic differences. The effect in women (median survival 15.7 months with the combination versus 7.5 months on cisplatin alone), however, was larger than the effect in males (median survival 11 versus 9.4 respectively). As with any exploratory analysis, it is not clear whether this difference is real or is a chance finding.

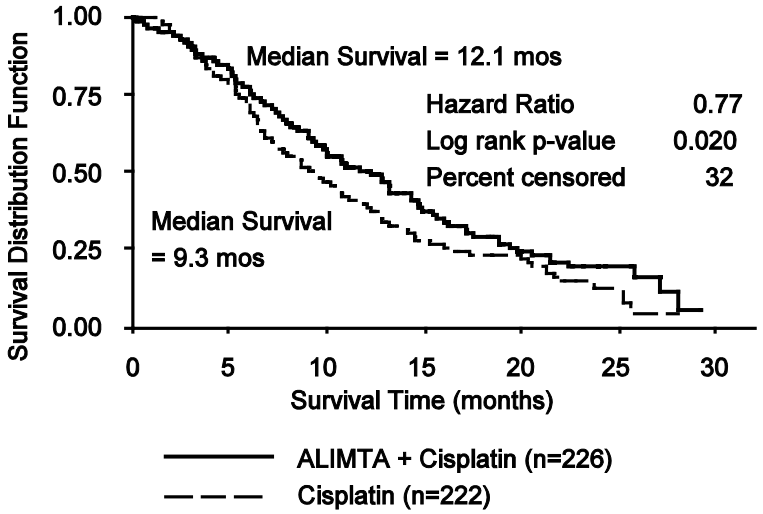


Figure 6: Kaplan-Meier Estimates of Survival Time for ALIMTA plus Cisplatin and Cisplatin Alone in all Randomized and Treated Patients.

Objective tumor response for malignant pleural mesothelioma is difficult to measure and response criteria are not universally agreed upon. However, based upon prospectively defined criteria, the objective tumor response rate for ALIMTA plus cisplatin was greater than the objective tumor response rate for cisplatin alone. There was also improvement in lung function (forced vital capacity) in the ALIMTA plus cisplatin arm compared to the control arm.

Patients who received full supplementation with folic acid and vitamin B_{12} during study therapy received a median of 6 and 4 cycles in the ALIMTA/cisplatin (N=168) and cisplatin (N=163) arms, respectively. Patients who never received folic acid and vitamin B_{12} during study therapy received a median of 2 cycles in both treatment arms (N=32 and N=38 for the ALIMTA/cisplatin and cisplatin arm, respectively). Patients receiving ALIMTA in the fully supplemented group received a relative dose intensity of 93% of the protocol specified ALIMTA dose intensity; patients treated with cisplatin in the same group received 94% of the projected dose intensity. Patients treated with cisplatin alone had a dose intensity of 96%.

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ALIMTA, pemetrexed for injection, is available in sterile single-use vials containing 100 mg pemetrexed.
NDC 0002-7640-01 (VL7640): single-use vial with ivory flip-off cap individually packaged in a carton.
ALIMTA, pemetrexed for injection, is available in sterile single-use vials containing 500 mg pemetrexed.
NDC 0002-7623-01 (VL7623): single-use vial with ivory flip-off cap individually packaged in a carton.

16.2 Storage and Handling

ALIMTA, pemetrexed for injection, should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Chemical and physical stability of reconstituted and infusion solutions of ALIMTA were demonstrated for up to 24 hours following initial reconstitution, when stored refrigerated, 2-8°C (36-46°F) When prepared as directed, reconstituted and infusion solutions of ALIMTA contain no antimicrobial preservatives. Discard unused portion *[see Dosage and Administration (2.5)]*.

ALIMTA is not light sensitive.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (PPI)

Instruct patients to read the patient package insert before initiating ALIMTA.

- Instruct patients on the need for folic acid and vitamin B_{12} supplementation to reduce treatment-related hematologic and gastrointestinal toxicity and of the need for corticosteroids to reduce treatment-related dermatologic toxicity *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.
- Inform patients of the risk of low blood cell counts and instruct them to immediately contact their physician for signs of infection, including fever, bleeding or symptoms of anemia.
- Instruct patients to contact their physician if persistent vomiting, diarrhea, or signs of dehydration appear.
- Instruct patients to inform their physician of all concomitant prescription or over-the-counter medications they are taking, particularly those for pain or inflammation such as non-steroidal anti-inflammatory drugs *[see Drug Interactions (7.1)]*.

Literature revised: Month dd, yyyy

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PATIENT INFORMATION
ALIMTA® (uh-LIM-tuh)
(pemetrexed for injection)

Read the Patient Information that comes with ALIMTA before you start treatment and each time you get treated with ALIMTA. There may be new information. This leaflet does not take the place of talking to your doctor about your medical condition or treatment. Talk to your doctor if you have any questions about ALIMTA.

What is ALIMTA?

ALIMTA is a treatment for:

- **Malignant pleural mesothelioma.** This cancer affects the inside lining of the chest cavity. ALIMTA is given with cisplatin, another anti-cancer medicine (chemotherapy).
- **Nonsquamous non-small cell lung cancer.** This cancer is a disease in which malignant (cancer) cells form in the tissues of the lung. If you are having initial treatment for your lung cancer, ALIMTA may be given alone or in combination with another chemotherapy drug. If this is the first time you have been treated for your lung cancer, ALIMTA may be given with another anti-cancer drug called cisplatin. If you have completed initial treatment for your lung cancer, ALIMTA may be given alone immediately following your initial treatment. If you are being treated because your cancer has come back or you had trouble tolerating a prior treatment, ALIMTA may be given alone. Your doctor will speak to you about whether ALIMTA is appropriate for your specific type of non-small cell lung cancer.

To lower your chances of side effects of ALIMTA, you must also take folic acid and vitamin B_{12} prior to and during your treatment with ALIMTA. Your doctor will prescribe a medicine called a "corticosteroid" to take for 3 days during your treatment with ALIMTA.

In children, ALIMTA has not been shown to be effective. No important differences in side effects were seen in children compared to adults (see "**What are the possible side effects of ALIMTA?**").

What should I tell my doctor before taking ALIMTA?

Tell your doctor about all of your medical conditions, including if you:

- **are pregnant or planning to become pregnant.** ALIMTA may harm your unborn baby.
- **are breastfeeding.** It is not known if ALIMTA passes into breast milk. You should stop breastfeeding once you start treatment with ALIMTA.
- **are taking other medicines,** including prescription and nonprescription medicines, vitamins, and herbal supplements. ALIMTA and other medicines may affect each other causing serious side effects. Especially, tell your doctor if you are taking medicines called "nonsteroidal anti-inflammatory drugs" (NSAIDs) for pain or swelling. There are many NSAID medicines. If you are not sure, ask your doctor or pharmacist if any of your medicines are NSAIDs.

How is ALIMTA given?

- ALIMTA is slowly infused (injected) into a vein. The injection or infusion will last about 10 minutes. You will usually receive ALIMTA once every 21 days (3 weeks).
- If you are being treated with ALIMTA and cisplatin for the initial treatment of either mesothelioma or non-small cell lung cancer, ALIMTA will be given first as a 10 minute infusion into your vein and cisplatin (another anti-cancer drug) will also be given through your vein starting about 30 minutes after ALIMTA and ending about 2 hours later.
- If you have completed initial treatment for your non-small cell lung cancer, you may receive ALIMTA alone, given as a 10 minute infusion into your vein.
- If you are being treated because your non-small cell lung cancer has returned, you may receive ALIMTA alone, given as a 10 minute infusion into your vein.

- Your doctor will prescribe a medicine called a "corticosteroid" to take for 3 days during your treatment with ALIMTA.
- **It is very important to take folic acid and vitamin B_{12} during your treatment with ALIMTA to lower your chances of harmful side effects.** You must start taking 400-1000 micrograms of folic acid every day for at least 5 days out of the 7 days before your first dose of ALIMTA. You must keep taking folic acid every day during the time you are getting treatment with ALIMTA and for 21 days after your last treatment. You can get folic acid vitamins over-the-counter. Folic acid is also found in many multivitamin pills. Ask your doctor or pharmacist for help if you are not sure how to choose a folic acid product. Your doctor will give you vitamin B_{12} injections while you are getting treatment with ALIMTA. You will get your first vitamin B_{12} injection during the week before your first dose of ALIMTA, and then about every 9 weeks during treatment.
- You will have regular blood tests before and during your treatment with ALIMTA. Your doctor may adjust your dose of ALIMTA or delay treatment based on the results of your blood tests and on your general condition.

What should I avoid while taking ALIMTA?

- **Women who can become pregnant should not become pregnant during treatment with ALIMTA.** ALIMTA may harm the unborn baby.
- **Ask your doctor before taking medicines called NSAIDs.** There are many NSAID medicines. If you are not sure, ask your doctor or pharmacist if any of your medicines are NSAIDs.

What are the possible side effects of ALIMTA?

Most patients taking ALIMTA will have side effects. Sometimes it is not always possible to tell whether ALIMTA, another medicine, or the cancer itself is causing these side effects. **Call your doctor right away if you have a fever, chills, diarrhea, or mouth sores.** These symptoms could mean you have an infection which may be severe and could lead to death.

The most common side effects of ALIMTA when given alone or in combination with cisplatin are:

- **Stomach upset, including nausea, vomiting, and diarrhea.** You can obtain medicines to help control some of these symptoms. Call your doctor if you get any of these symptoms.
- **Low blood cell counts:**
  - **Low red blood cells.** Low red blood cells may make you feel tired, get tired easily, appear pale, and become short of breath.
  - **Low white blood cells.** Low white blood cells may give you a greater chance for infection. If you have a fever (temperature above 100.4°F) or other signs of infection, call your doctor right away.
  - **Low platelets.** Low platelets give you a greater chance for bleeding. Your doctor will do blood tests to check your blood counts before and during treatment with ALIMTA.
- **Tiredness.** You may feel tired or weak for a few days after your ALIMTA treatments. If you have severe weakness or tiredness, call your doctor.
- **Redness or sores in your mouth, throat, on your lips, or in the tube that connects your throat and stomach (esophagus).** Redness and sores may begin a few days after your ALIMTA treatment. Call your doctor if this happens, or if you have pain or trouble drinking or swallowing food.
- **Loss of appetite.** You may lose your appetite and lose weight during your treatment. Talk to your doctor if this is a problem for you.
- **Rash.** You may get a rash or itching during treatment. These reactions usually appear between treatments with ALIMTA and usually go away before the next treatment. Skin reactions or rashes that include blistering or peeling may be severe and could lead to death. Call your doctor if you have any of these symptoms.

Talk with your doctor, nurse, or pharmacist about any side effect that bothers you or that doesn't go away.

These are not all the side effects of ALIMTA. For more information, ask your doctor, nurse, or pharmacist.

General information about ALIMTA

Medicines are sometimes prescribed for conditions other than those listed in patient information leaflets. ALIMTA was prescribed for your medical condition.

This leaflet summarizes the most important information about ALIMTA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about ALIMTA that is written for health professionals. You can also call 1-800-LILLY-RX (1-800-545-5979) or visit www.ALIMTA.com.

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