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 disodium) Injection, Powder, Lyophilized, For Solution for Intravenous use

Initial U.S. Approval: 2004

---------- RECENT MAJOR CHANGES ----------

Indications and Usage, Non-Small Cell Lung Cancer — Combination with Cisplatin (1.1) 09/2008

Indications and Usage, Non-Small Cell Lung Cancer — Single-Agent (1.2) 09/2008

Dosage and Administration Combination Use with Cisplatin (2.1) 09/2008

---------- INDICATIONS AND USAGE ----------

ALIMTA® is a folate analog metabolic inhibitor indicated for:

- Nonsquamous Non-Small Cell Lung Cancer: initial treatment in combination with cisplatin. (1.1)
- Nonsquamous Non-Small Cell Lung Cancer as a single-agent after prior chemotherapy (1.2)
- Mesothelioma: in combination with cisplatin (1.3)

---------- 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)
- 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: Instruct patients to take folic acid and vitamin B_{12}. Pretreatment with dexamethasone or equivalent reduces cutaneous reaction. (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 begin next 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 ibuprofen or other 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:09/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 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. ALIMTA is not indicated for treatment of patients with squamous cell non-small cell lung cancer.

1.2 Non-Small Cell Lung Cancer — Single-Agent

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

1.3 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.

2 DOSAGE AND ADMINISTRATION

2.1 Combination Use with Cisplatin

Non-Small Cell Lung Cancer and 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. Patients should receive appropriate hydration prior to and/or after receiving cisplatin. See cisplatin package insert for more information.

2.2 Single-Agent Use

Non-Small Cell Lung Cancer

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

Vitamin Supplementation

To reduce toxicity, patients treated with ALIMTA must be instructed to take a low-dose oral folic acid preparation or multivitamin with 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 (1) 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 mcg, and the dose of vitamin B_{12} was 1000 mcg. The most commonly used dose of oral folic acid in clinical trials was 400 mcg *[see Warnings and Precautions (5.1)]*.

Corticosteroid

Skin rash has been reported more frequently in patients not pretreated with a corticosteroid. Pretreatment 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 *[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 (both drugs).
Nadir platelets <50,000/mm^3 without bleeding regardless of nadir ANC.	75% of previous dose (both drugs).
Nadir platelets <50,000/mm^3 with bleeding[a], regardless of nadir ANC.	50% of previous dose (both drugs).

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[c] 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).

[c] Except Grade 3 transaminase elevation, for which no dose reduction is needed.

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 (except Grade 3 transaminase elevations) 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:

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

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 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 at refrigerated or ambient room temperature [see USP Controlled Room Temperature] and lighting. 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 or to any other ingredient used in the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Premedication Regimen

Need for Folate and Vitamin B_{12} Supplementation

Patients treated with ALIMTA must be instructed to take folic acid and vitamin B_{12} as a prophylactic measure to reduce treatment-related hematologic and GI toxicity *[see Dosage and Administration (2.3)]*. In clinical studies, less overall toxicity and reductions in Grade 3/4 hematologic and nonhematologic 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.

Corticosteroid Supplementation

Skin rash has been reported more frequently in patients not pretreated with a corticosteroid in clinical trials. Pretreatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction *[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 with Mild to Moderate Renal Insufficiency

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

5.5 Required Laboratory Monitoring

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 *[see Dosing 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 Pregnancy (8.1)]*

5.7 Third Space Fluid

The effect of third space fluid, such as pleural effusion and ascites, on ALIMTA is unknown. In patients with clinically

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) — 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

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