

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/m² i.v. on Day 1 of each 21-day cycle in combination with cisplatin 75 mg/m² 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/m² 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 B₁₂. 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/mm³, platelets ≥100,000 cells/mm³, 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:10/2008

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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/m² administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle. The recommended dose of cisplatin is 75 mg/m² 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 UseNon-Small Cell Lung Cancer

The recommended dose of ALIMTA is 500 mg/m² administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle.

2.3 Premedication RegimenVitamin 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 B₁₂ during the week preceding the first dose of ALIMTA and every 3 cycles thereafter. Subsequent vitamin B₁₂ 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 B₁₂ 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 RecommendationsMonitoring

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/mm³, the platelet count is $\geq 100,000$ cells/mm³, 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 $\geq 50,000$ /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). |

^a These criteria meet the CTC version 2.0 (NCI 1998) definition of \geq CTC Grade 2 bleeding.

If patients develop nonhematologic toxicities (excluding neurotoxicity) \geq 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 \geq 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:

$$\begin{aligned} \text{Males:} & \quad \frac{[140 - \text{Age in years}] \times \text{Actual Body Weight (kg)}}{72 \times \text{Serum Creatinine (mg/dL)}} = \text{mL/min} \\ \text{Females:} & \quad \text{Estimated creatinine clearance for males} \times 0.85 \end{aligned}$$

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.

- 98 5. An appropriate quantity of the reconstituted ALIMTA solution must be further diluted into a solution of 0.9% Sodium
 99 Chloride Injection (preservative free), so that the total volume of solution is 100 ml. ALIMTA is administered as an
 100 intravenous infusion over 10 minutes.
 101 6. Chemical and physical stability of reconstituted and infusion solutions of ALIMTA were demonstrated for up to 24 hours
 102 following initial reconstitution, when stored at refrigerated or ambient room temperature [see USP Controlled Room
 103 Temperature] and lighting. When prepared as directed, reconstitution and infusion solutions of ALIMTA contain no
 104 antimicrobial preservatives. Discard any unused portion.

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

110 3 DOSAGE FORMS AND STRENGTHS

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

113 4 CONTRAINDICATIONS

114 ALIMTA is contraindicated in patients who have a history of severe hypersensitivity reaction to pemetrexed or to any other
 115 ingredient used in the formulation.

116 5 WARNINGS AND PRECAUTIONS

117 5.1 Premedication Regimen

118 Need for Folate and Vitamin B₁₂ Supplementation

119 Patients treated with ALIMTA must be instructed to take folic acid and vitamin B₁₂ as a prophylactic measure to reduce
 120 treatment-related hematologic and GI toxicity [see *Dosage and Administration* (2.3)]. In clinical studies, less overall toxicity and
 121 reductions in Grade 3/4 hematologic and nonhematologic toxicities such as neutropenia, febrile neutropenia, and infection with Grade
 122 3/4 neutropenia were reported when pretreatment with folic acid and vitamin B₁₂ was administered.

123 Corticosteroid Supplementation

124 Skin rash has been reported more frequently in patients not pretreated with a corticosteroid in clinical trials. Pretreatment with
 125 dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction [see *Dosage and Administration* (2.3)].

126 5.2 Bone Marrow Suppression

127 ALIMTA can suppress bone marrow function, as manifested by neutropenia, thrombocytopenia, and anemia (or pancytopenia)
 128 [see *Adverse Reactions* (6.1)]; myelosuppression is usually the dose-limiting toxicity. Dose reductions for subsequent cycles are based
 129 on nadir ANC, platelet count, and maximum nonhematologic toxicity seen in the previous cycle [see *Dosage and Administration*
 130 (2.4)].

131 5.3 Decreased Renal Function

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

136 One patient with severe renal impairment (creatinine clearance 19 mL/min) who did not receive folic acid and vitamin B₁₂
 137 died of drug-related toxicity following administration of ALIMTA alone.

138 5.4 Use with Non-Steroidal Anti-Inflammatory Drugs with Mild to Moderate Renal Insufficiency

139 Caution should be used when administering ibuprofen concurrently with ALIMTA to patients with mild to moderate renal
 140 insufficiency (creatinine clearance from 45 to 79 mL/min). Other NSAIDs should also be used with caution [see *Drug Interactions*
 141 (7.1)].

142 5.5 Required Laboratory Monitoring

143 Patients should not begin a new cycle of treatment unless the ANC is ≥ 1500 cells/mm³, the platelet count is
 144 $\geq 100,000$ cells/mm³, and creatinine clearance is ≥ 45 mL/min [see *Dosing and Administration* (2.4)].

145 5.6 Pregnancy Category D

146 Based on its mechanism of action, ALIMTA can cause fetal harm when administered to a pregnant woman. Pemetrexed
 147 administered intraperitoneally to mice during organogenesis was embryotoxic, fetotoxic and teratogenic in mice at greater than
 148 1/833rd the recommended human dose. If ALIMTA is used during pregnancy, or if the patient becomes pregnant while taking this
 149 drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid
 150 becoming pregnant. Women should be advised to use effective contraceptive measures to prevent pregnancy during treatment with
 151 ALIMTA. [see *Pregnancy* (8.1)]

152 5.7 Third Space Fluid

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

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 $\geq 20\%$) during therapy with ALIMTA as a single-agent were fatigue, nausea, and anorexia. Additional common adverse reactions (incidence $\geq 20\%$) 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 B₁₂.

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

184 *Metabolism and Nutrition* — increased AST, increased ALT

185 *Renal* — creatinine clearance decrease, renal failure

186 *Special Senses* — conjunctivitis

187 **Incidence Less than 1%**

188 *Cardiovascular* — arrhythmia

189 *General Disorders* — chest pain

190 *Metabolism and Nutrition* — increased GGT

191 *Neurology* — motor neuropathy

192 **Non-Small Cell Lung Cancer (NSCLC) — Single-Agent**

193 Table 5 provides the frequency and severity of adverse reactions that have been reported in >5% of 265 patients randomly
194 assigned to receive single-agent ALIMTA with folic acid and vitamin B₁₂ supplementation and 276 patients randomly assigned to
195 receive single-agent docetaxel. All patients were diagnosed with locally advanced or metastatic NSCLC and received prior
196 chemotherapy.

197 **Table 5: 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 |

199 ^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
200 to ALIMTA.

201 ^b Refer to NCI CTC Criteria for lab values for each Grade of toxicity (version 2.0).

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

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

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

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

208 **Incidence 1% to 5%**

209 *Body as a Whole* — abdominal pain, allergic reaction/hypersensitivity, febrile neutropenia, infection

210 *Dermatology/Skin* — erythema multiforme

211 *Neurology* — motor neuropathy, sensory neuropathy

212 *Renal* — increased creatinine

213 **Incidence Less than 1%**

214

Cardiovascular — supraventricular arrhythmias

Malignant Pleural Mesothelioma (MPM)

Table 6 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 chemo-naïve patients were fully supplemented with folic acid and vitamin B₁₂.

Table 6: 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

Table 7 compares the incidence (percentage of patients) of CTC Grade 3/4 toxicities in patients who received vitamin supplementation with daily folic acid and vitamin B₁₂ 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 7: 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%).

Subpopulations

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%).

Phase 2 Studies

Clinically relevant Grade 3 and Grade 4 laboratory toxicities were similar between integrated Phase 2 results from three single-agent ALIMTA studies (N=164) and the Phase 3 single-agent ALIMTA study described above, with the exception of neutropenia (12.8% versus 5.3%, respectively) and alanine transaminase elevation (15.2% versus 1.9%, respectively). These differences were likely due to differences in the patient population, since the Phase 2 studies included chemo-naïve and heavily pretreated breast cancer patients with pre-existing liver metastases and/or abnormal baseline liver function tests.

6.2 Post-Marketing 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 have occurred with ALIMTA when used as a single-agent and in combination therapies.

Gastrointestinal — colitis

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

7 DRUG INTERACTIONS

7.1 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Ibuprofen

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 \geq 80 mL/min). 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) [see *Clinical Pharmacology* (12.3)].

Other NSAIDs

Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of, and 2 days following administration of ALIMTA.

In the absence of data regarding potential interaction between ALIMTA and NSAIDs with longer half-lives, all 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 an NSAID 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/m² basis), and cleft palate (1/33rd the recommended intravenous human dose on a mg/m² 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

The safety and effectiveness of ALIMTA in pediatric patients have not been established.

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. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. 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)*].

In the initial treatment non-small cell lung cancer clinical trial, 37.7% of patients treated with ALIMTA plus cisplatin were ≥65 years and Grade 3/4 neutropenia was greater as compared to patients <65 years (19.9% versus 12.2%). For patients <65 years, the HR for overall survival was 0.96 (95% CI: 0.83, 1.10) and for patients ≥65 years the HR was 0.88 (95% CI: 0.74, 1.06) in the intent to treat population.

In the previously treated non-small cell lung cancer trial, 29.7% patients treated with ALIMTA were ≥65 years and Grade 3/4 hypertension was greater as compared to patients <65 years. For patients <65 years, the HR for overall survival was 0.95 (95% CI: 0.76, 1.19), and for patients ≥65 years the HR was 1.15 (95% CI: 0.79, 1.68) in the intent to treat population.

The mesothelioma trial included 36.7% patients treated with ALIMTA plus cisplatin that were ≥65 years, and Grade 3/4 fatigue, leukopenia, neutropenia, and thrombocytopenia were greater as compared to patients <65 years. For patients <65 years, the HR for overall survival was 0.71 (95% CI: 0.53, 0.96) and for patients ≥65 years, the HR was 0.85 (95% CI: 0.59, 1.22) in the intent to treat population.

8.6 Patients with Hepatic Impairment

There was no effect of elevated AST, ALT, or total bilirubin on the pharmacokinetics of pemetrexed [see *Clinical Pharmacology (12.3)*].

Dose adjustments based on hepatic impairment experienced during treatment with ALIMTA are provided in Table 2 [see *Dosage and Administration (2.4)*].

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

In the previously untreated non-small cell lung cancer trial, 70% of patients were males and 30% females. For males the HR for overall survival was 0.97 (95% CI: 0.85, 1.10) and for females the HR was 0.86 (95% CI: 0.70, 1.06) in the intent to treat population.

In the previously treated non-small cell lung cancer trial, 72% of patients were males and 28% females. For males the HR for overall survival was 0.95 (95% CI: 0.76, 1.19) and for females the HR was 1.28 (95% CI: 0.86, 1.91) in the intent to treat population.

In the mesothelioma trial, 82% of patients were males and 18% females. For males the HR for overall survival was 0.85 (95% CI: 0.66, 1.09) and for females the HR was 0.48 (95% CI: 0.27, 0.85) in the intent to treat population.

8.9 Race

In the previously untreated non-small cell lung cancer trial, 78% of patients were Caucasians, 13% East/Southeast Asians, and 9% others. For Caucasians, the HR for overall survival was 0.92 (95% CI: 0.82, 1.04), for East/Southeast Asians the HR was 0.86 (95% CI: 0.61, 1.21), and for others the HR was 1.24 (95% CI: 0.84, 1.84) in the intent to treat population.

In the previously treated non-small cell lung cancer trial, 71% of patients were Caucasians and 29% others. For Caucasians the HR for overall survival was 0.91 (95% CI: 0.73, 1.15) and for others the HR was 1.27 (95% CI: 0.87, 1.87) in the intent to treat population.

In the mesothelioma trial, 92% of patients were Caucasians and 8% others. For Caucasians, the HR for overall survival was 0.77 (95% CI: 0.61, 0.97) and for others the HR was 0.86 (95% CI: 0.39, 1.90) in the intent to treat population.

10 OVERDOSAGE

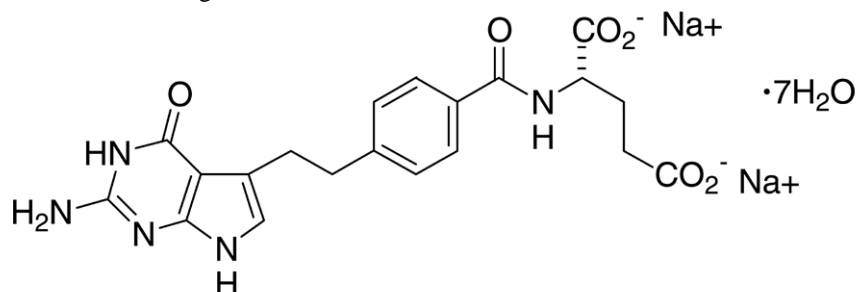
There have been few cases of ALIMTA overdose. Reported toxicities included neutropenia, anemia, thrombocytopenia, mucositis, and rash. Anticipated complications of overdose include bone marrow suppression as manifested by neutropenia, thrombocytopenia, and anemia. In addition, infection with or without 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/m², intravenously once, followed by leucovorin, 50 mg/m², 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 C₂₀H₁₉N₅Na₂O₆•7H₂O 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, 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 B₁₂ 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 B₁₂ 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/m² 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.

Effect of Age

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

Effect of Gender

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

Effect of Race

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)*].

Pediatric

Pediatric patients were not included in clinical trials.

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 B₁₂ 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/m² 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 chemo-naïve 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/m² with cisplatin administered intravenously at a dose of 75 mg/m² after ALIMTA administration, on Day 1 of each 21-day cycle. Gemcitabine was administered at a dose of 1250 mg/m² on Day 1 and Day 8, and cisplatin was administered intravenously at a dose of 75 mg/m² 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 B₁₂, and dexamethasone [*see Dosage and Administration (2.3)*].

Patient demographics of the intent to treat (ITT) population are shown in Table 8. The demographics and disease characteristics were well balanced.

Table 8: Summary of Patient Characteristics in Study of NSCLC — Combination with Cisplatin

| 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 9: Efficacy of ALIMTA plus Cisplatin versus Gemcitabine plus Cisplatin in First-line 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.

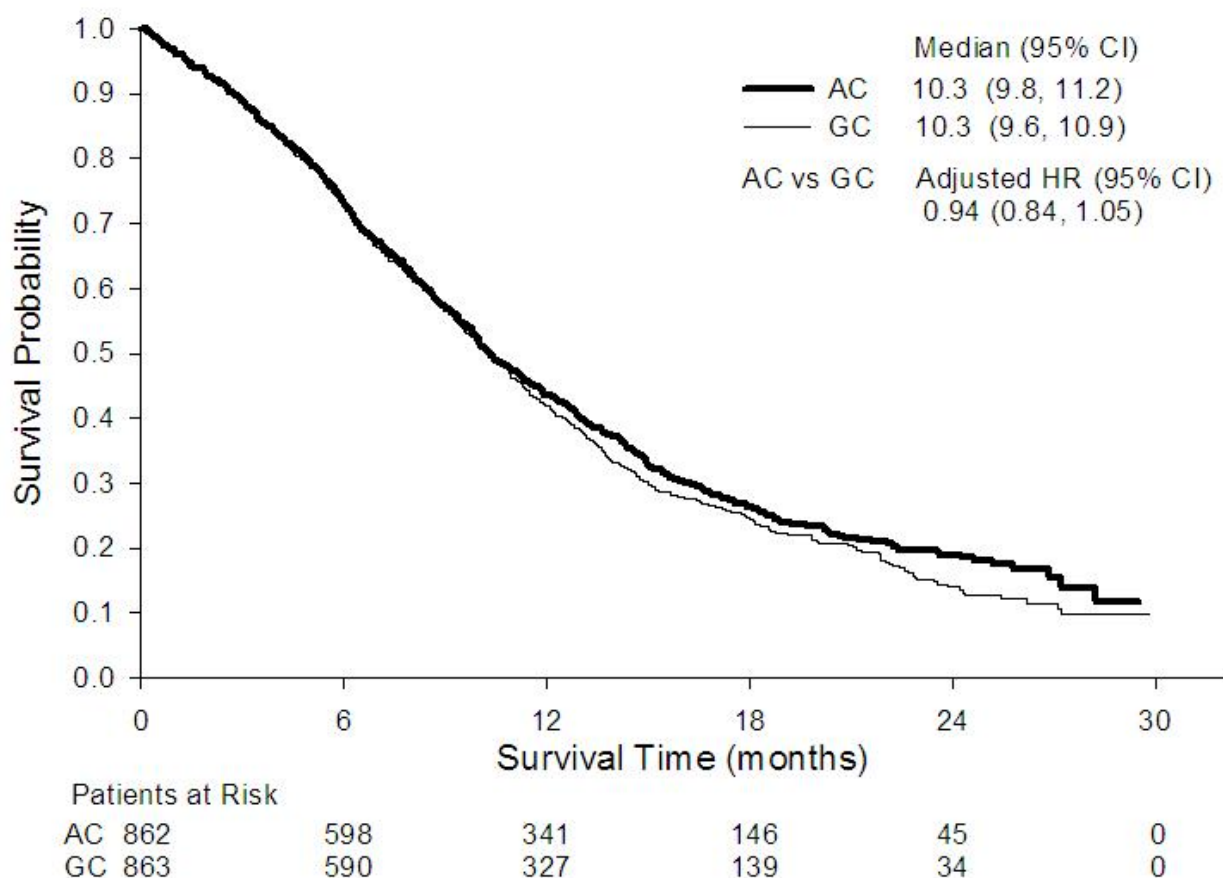


Figure 1: Kaplan-Meier Curves for Overall Survival ALIMTA plus Cisplatin (AC) versus Gemcitabine plus Cisplatin (GC) in NSCLC — ITT Population.

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 10. This difference in treatment effect for ALIMTA based on histology was also observed in the single-agent, second-line study [see *Clinical Studies (14.2)*].

Table 10: Overall Survival of ALIMTA plus Cisplatin versus Gemcitabine plus Cisplatin in NSCLC — Histologic Subgroups, ITT Population

| 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.

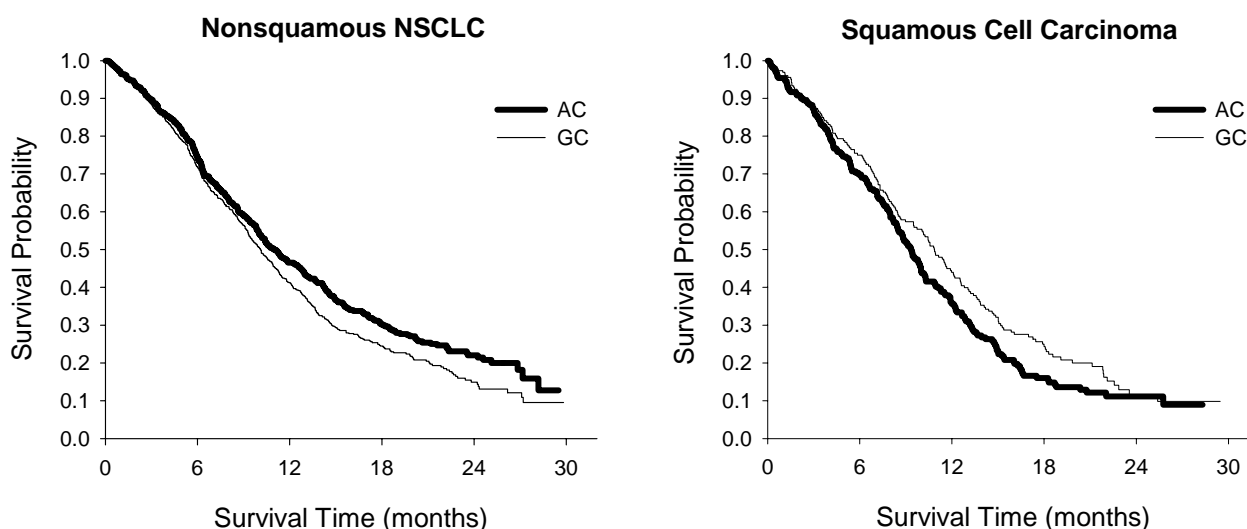


Figure 2: Kaplan-Meier Curves for Overall Survival ALIMTA plus Cisplatin (AC) versus Gemcitabine plus Cisplatin (GC) in NSCLC — Nonsquamous NSCLC and Squamous Cell Carcinoma.

14.2 Non-Small Cell Lung Cancer — Single-Agent Use

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/m² and docetaxel was administered at 75 mg/m² 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 B₁₂. 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 11.

Table 11: 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 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 12). The study did not show an overall survival superiority of ALIMTA.

Table 12: 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 13. This difference in treatment effect for ALIMTA based on histology was also observed in the first-line combination study [see *Clinical Studies (14.1)*].

Table 13: Overall Survival of ALIMTA versus Docetaxel in NSCLC — Histologic Subgroups, ITT Population

| 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.

14.3 Malignant Pleural Mesothelioma

A multi-center, randomized, single-blind study in 448 chemo-naïve 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/m² and cisplatin was administered intravenously over 2 hours at a dose of 75 mg/m² 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 B₁₂ 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 B₁₂ 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 14.

Table 14: 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 15 summarizes 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 15: 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.

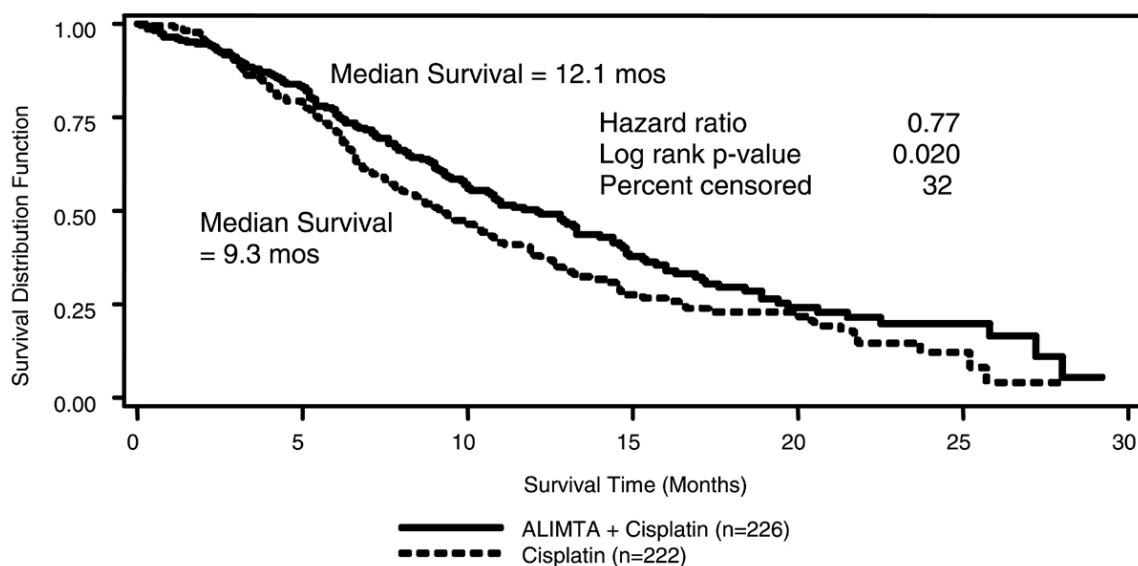


Figure 3: Kaplan-Meier Estimates of Survival Time for ALIMTA plus Cisplatin and Cisplatin Alone in all Randomized and Treated Patients.

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 B₁₂ 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 B₁₂ 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%.

15 REFERENCES

1. Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. NIOSH Alert 2004-165.
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999.
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3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006;63:1172-1193.
4. Polovich, M., White, J. M., & Kelleher, L. O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

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), or at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. When prepared as directed, reconstituted and infusion solutions of ALIMTA contain no antimicrobial preservatives. Discard unused portion.

ALIMTA is not light sensitive.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling

17.1 Need for Folic Acid and Vitamin B₁₂

Patients treated with ALIMTA must be instructed to take folic acid and vitamin B₁₂ as a prophylactic measure to reduce treatment-related hematologic and gastrointestinal toxicity [see *Dosage and Administration (2.3)*].

17.2 Low Blood Cell Counts

Patients should be adequately informed of the risk of low blood cell counts and instructed to immediately contact their physician should any sign of infection develop including fever. Patients should also contact their physician if bleeding or symptoms of anemia occur.

17.3 Gastrointestinal Effects

Patients should be instructed to contact their physician if persistent vomiting, diarrhea, or signs of dehydration appear.

17.4 Concomitant Medications

Patients should be instructed to inform the physician if they are taking any concomitant prescription or over-the-counter medications including those for pain or inflammation such as non-steroidal anti-inflammatory drugs [see *Drug Interactions (7.1)*].

17.5 FDA Approved Patient Labeling

Patients should be instructed to read the patient package insert carefully.

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