DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-462

Eli Lilly & Company
Attention: John F. Worzalla
Regulatory Research Scientist, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Mr. Worzalla:

Please refer to your new drug application (NDA) dated September 29, 2003, received September 30, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alimta® (pemetrexed, LY231514).

We acknowledge receipt of your submissions dated October 24, November 22, December 6, 2002; January 10, 28, February 13, March 24, 27, April 3, May 9, 12, 29, June 18, 26, 30, July 29, 30, August 8, 15, 21, 28, September 2, 3, 4, 9, 12, 15, 16, 19, 22, 29, October 6, 7, 20, November 4, 5, 6, 14, 18, 24, 26, December 1, 4, 5, 10, 11, 12, 15, 16, 29, 2003, and January 12, 2004.

This new drug application provides for the use of Alimta® (pemetrexed, LY231514) in the treatment of patients with malignant pleural mesothelioma whose disease is either unresectable or who are otherwise not candidates for curative surgery.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon attached labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and the patient package insert). Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-462**." Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Oncology Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising
And Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The Med-Watch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Patty Garvey, Regulatory Project Manager, at (301) 594-5766.

Sincerely,
{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: labeling

FDA News

FOR IMMEDIATE RELEASE
P04-14
February 5, 2004

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA Approves First Drug for Rare Type of Cancer

The Food and Drug Administration (FDA) today approved Alimta (pemetrexed disodium) for use in combination with cisplatin for the treatment of patients with malignant pleural mesothelioma-a rare type of cancer. Alimta received a priority review and is designated as an orphan drug. It is the first drug approved for this condition.

Cancer of the mesothelium, a membrane that covers and protects most of the internal organs of the body is rare; about 2,000 new cases are diagnosed in the United States each year. This form of cancer is usually associated with a history of asbestos exposure. Asbestos fibers lodged in the lung attach to the outer lung lining and chest wall, causing tumors to grow. By the time symptoms appear, the disease is usually advanced, and patients live, on average, nine to thirteen months following diagnosis.

"Up to now there has been no effective treatment for treating mesothelioma. Alimta offers new promise in treating this fatal cancer," said FDA Commissioner Mark B. McClellan M.D., Ph.D, "and its quick approval demonstrates FDA's commitment to making safe and effective products available as soon as possible."

The effectiveness of Alimta was established in one randomized clinical trial comparing the effects of treatment with Alimta given with cisplatin to treatment with cisplatin alone. Patients receiving Alimta and cisplatin lived three months longer after randomization than patients given cisplatin alone (12 months vs. nine months). Alimta must be administered with vitamin B-12 and folic acid supplementation to decrease the incidence and severity of adverse effects.

The most common adverse reactions observed with use of Alimta are low white blood count, nausea, vomiting, fatigue, rash, and diarrhea. Patients and caregivers should be encouraged to report the onset of fever, chills, diarrhea, and mouth ulcers immediately, since these symptoms could be a sign of infection, resulting from bone marrow suppression by the drug. Orphan drugs are developed to treat rare diseases, that is, conditions that affect fewer than 200,000 people in the U.S. The Orphan Drug Act provides a seven-year period of exclusive marketing for the drug to the first sponsor who obtains marketing approval for a designated orphan drug.

Alimta will be distributed by Eli Lilly and Company, Indianapolis, Ind.

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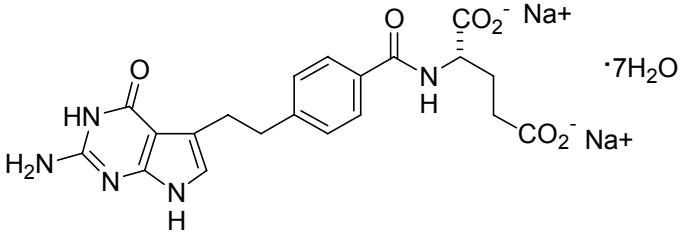
Additional Information

0.75 PA 9300 FSAMP

ALIMTA®
pemetrexed
for injection

DESCRIPTION

ALIMTA®, pemetrexed for injection, is an antifolate antineoplastic agent that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication. 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 $C_{20}H_{19}N_5Na_2O_6 \cdot 7H_2O$ 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 500-mg vial of ALIMTA contains pemetrexed disodium equivalent to 500 mg pemetrexed and 500 mg of mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Pemetrexed is an antifolate containing the pyrrolopyrimidine-based nucleus that exerts its antineoplastic activity 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), all folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is transported into cells by both the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is converted to polyglutamate forms by the enzyme folyl polyglutamate synthase. 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, to a lesser extent, in normal tissues. Polyglutamated metabolites have an increased intracellular half-life resulting in prolonged drug action in malignant cells.

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 pemetrexed 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, is inversely proportional to the systemic exposure of ALIMTA. 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 μg•hr/mL. Return to baseline ANC occurred 4.2 to 7.5 days after the nadir over the same range of exposures.

Pharmacokinetics

The pharmacokinetics of pemetrexed 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 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 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 clearance decreases, and exposure (AUC) increases, as renal function decreases. 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. 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.

Drug Interactions

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

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. No studies were conducted to determine the cytochrome P450 isozyme induction potential of pemetrexed, because ALIMTA used as recommended (once every 21 days) would not be expected to cause any significant enzyme induction.

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.

Ibuprofen — Daily ibuprofen doses of 400 mg qid 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** *under* **PRECAUTIONS**).

Special Populations

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

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

Pediatric — Pediatric patients were not included in clinical trials.

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

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.

Hepatic Insufficiency —There was no effect of elevated AST (SGOT), ALT (SGPT), or total bilirubin on the pharmacokinetics of pemetrexed. However, studies of hepatically impaired patients have not been conducted (*see* **PRECAUTIONS**).

Renal Insufficiency — Pharmacokinetic analyses of pemetrexed included 127 patients with reduced renal function. Plasma clearance of pemetrexed in the presence of cisplatin decreases as renal function decreases, with 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* **DOSAGE AND ADMINISTRATION).**

CLINICAL STUDIES

Malignant Pleural Mesothelioma — The safety and efficacy of ALIMTA have been evaluated in chemonaive patients with malignant pleural mesothelioma (MPM) in combination with cisplatin.

Randomized Trial: A multi-center, randomized, single-blind study in 448 chemonaive patients with 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 112 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). Results in all patients and those fully supplemented were similar. Patient demographics are shown in Table 1.

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Table 1: Summary of Patient Characteristics

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 2 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 2: Efficacy of ALIMTA plus Cisplatin vs. 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*	0.020		0.051	

* 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. Exploratory demographic analyses showed no apparent differences in patients over or under 65. There were too few non-white patients to assess possible ethnic differences. The effect in women (median survival 15.7 months with the combination vs 7.5 months on cisplatin alone), however, was larger than the effect in males (median survival 11 vs 9.4 respectively). As with any exploratory analysis, it is not yet clear whether this difference is real or is a chance finding.

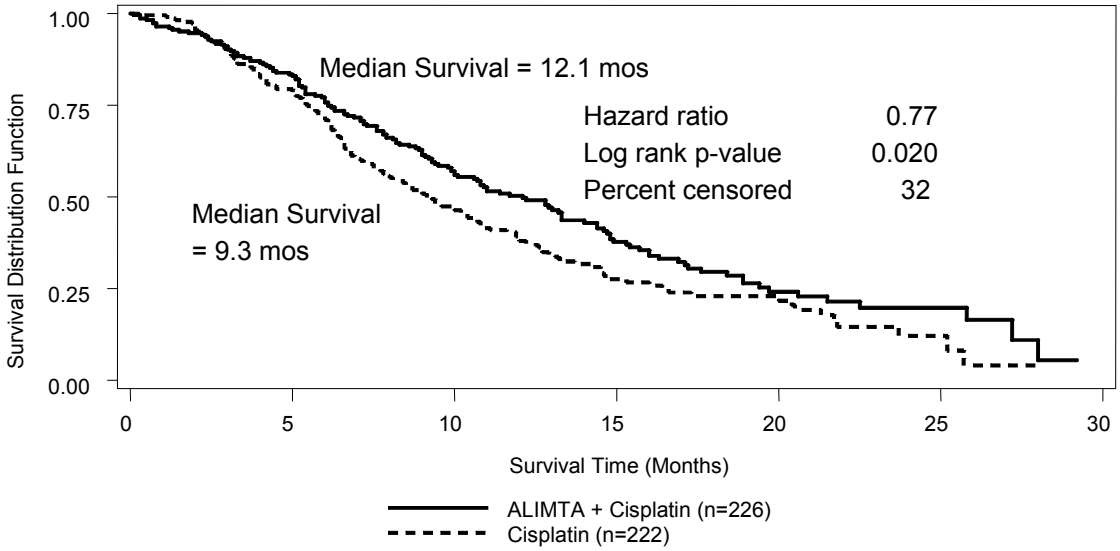

Figure 1: Kaplan-Meier Estimates of Survival Time for ALIMTA plus Cisplatin and Cisplatin Alone in all Randomized and Treated Patients.

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%.

INDICATIONS AND USAGE

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

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.

WARNINGS

Decreased Renal Function

ALIMTA is primarily eliminated unchanged by renal excretion. No dosage adjustment is needed in patients with creatinine clearance $\geq$ 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* **Dose Reduction Recommendations** *under* **DOSAGE AND ADMINISTRATION**).

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.

Bone Marrow Suppression

ALIMTA can suppress bone marrow function, manifested by neutropenia, thrombocytopenia, and anemia (*see* **ADVERSE REACTIONS**); 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* **Dose Reduction Recommendations** *under* **DOSAGE AND ADMINISTRATION**).

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**). 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.

Pregnancy Category D

ALIMTA may cause fetal harm when administered to a pregnant woman. Pemetrexed was fetotoxic and teratogenic in mice at i.v. doses of 0.2 mg/kg (0.6 mg/m^2) or 5 mg/kg (15 mg/m^2) when given on gestation days 6 through 15. Pemetrexed caused fetal malformations (incomplete ossification of talus and skull bone) at 0.2 mg/kg (about 1/833 the recommended i.v. human dose on a mg/m^2 basis), and cleft palate at 5 mg/kg (about 1/33 the recommended i.v. human dose on a mg/m^2 basis). Embryotoxicity was characterized by increased embryo-fetal deaths and reduced litter sizes. There are no studies of ALIMTA in pregnant women. Patients should be advised to avoid becoming pregnant. If ALIMTA is used during pregnancy, or if the patient becomes pregnant while taking ALIMTA, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

General

ALIMTA should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available. Treatment-related adverse events of ALIMTA seen in clinical trials have been reversible. Skin rash has been reported 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**).

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

Laboratory Tests

Complete blood cell counts, including platelet counts and periodic chemistry tests, 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.

Drug Interactions

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.

Although ibuprofen (400 mg qid) can be administered with ALIMTA in patients with normal renal function (creatinine clearance ≥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). 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.

Drug/Laboratory Test Interactions

None known.

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.

Pregnancy

Pregnancy Category D (*see* **WARNINGS**).

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, it is recommended that nursing be discontinued if the mother is treated with ALIMTA.

Pediatric Use

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

Geriatric Use

Dose adjustments based on age other than those recommended for all patients have not been necessary (*see* **Special Populations** *under* **CLINICAL PHARMACOLOGY** *and* **DOSAGE AND ADMINISTRATION**).

Gender

Dose adjustments based on gender other than those recommended for all patients have not been necessary (*see* **Special Populations** *under* **CLINICAL PHARMACOLOGY** *and* **DOSAGE AND ADMINISTRATION**).

Patients with Hepatic Impairment

Patients with bilirubin >1.5 times the upper limit of normal were excluded from clinical trials of ALIMTA. Patients with transaminase >3.0 times the upper limit of normal were routinely excluded from clinical trials if they had no evidence of hepatic metastases. Patients with

transaminase from 3 to 5 times the upper limit of normal were included in the clinical trial of ALIMTA if they had hepatic metastases.

Dose adjustments based on hepatic impairment experienced during treatment with ALIMTA are provided in Table 6 (*see* **Special Populations** *under* **CLINICAL PHARMACOLOGY** *and* **DOSAGE AND ADMINISTRATION**).

Patients with Renal Impairment

ALIMTA is known to be primarily excreted by the kidney. Decreased renal function will result in reduced clearance and greater exposure (AUC) to ALIMTA compared with patients with normal renal function. Cisplatin coadministration with ALIMTA has not been studied in patients with moderate renal impairment (*see* **Special Populations** *under* **CLINICAL PHARMACOLOGY**).

ADVERSE REACTIONS

In Table 3 adverse events occurring in at least 5% patients are shown along with important effects (renal failure, infection) occurring at lower rates. Adverse events equally or more common in the cisplatin group are not included. The adverse effects more common in the Alimta group were primarily hematologic effects, fever and infection, stomatitis/pharyngitis, and rash/desquamation.

Table 3: Adverse Events* in Fully Supplemented Patients Receiving ALIMTA plus Cisplatin in MPM

CTC Grades (% incidence)

	All Reported Adverse Events Regardless of Causality					
	ALIMTA/cis (N=168)			Cisplatin (N=163)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory						
Hematologic						
Neutropenia	58	19	5	16	3	1
Leukopenia	55	14	2	20	1	0
Anemia	33	5	1	14	0	0
Thrombocytopenia	27	4	1	10	0	0
Renal						
Creatinine elevation	16	1	0	12	1	0
Renal failure	2	0	1	1	0	0
Clinical						
Constitutional Symptoms						
Fatigue	80	17	0	74	12	1
Fever	17	0	0	9	0	0
Other constitutional symptoms	11	2	1	8	1	1
Cardiovascular General						
Thrombosis/embolism	7	4	2	4	3	1
Gastrointestinal						

Nausea	84	11	1	79	6	0
Vomiting	58	10	1	52	4	1
Constipation	44	2	1	39	1	0
Anorexia	35	2	0	25	1	0
Stomatitis/pharyngitis	28	2	1	9	0	0
Diarrhea without colostomy	26	4	0	16	1	0
Dehydration	7	3	1	1	1	0
Dysphagia/esophagitis/ odynophagia	6	1	0	6	0	0
Pulmonary						
Dyspnea	66	10	1	62	5	2
Pain						
Chest pain	40	8	1	30	5	1
Neurology						
Neuropathy/sensory	17	0	0	15	1	0
Mood alteration/ depression	14	1	0	9	1	0
Infection/Febrile Neutropenia						
Infection without neutropenia	11	1	1	4	0	0
Infection with Grade 3 or Grade 4 neutropenia	6	1	0	4	0	0
Infection/febrile neutropenia-other	3	1	0	2	0	0
Febrile neutropenia	1	1	0	1	0	0
Immune						
Allergic reaction/ hypersensitivity	2	0	0	1	0	0
Dermatology/Skin						
Rash/desquamation	22	1	0	9	0	0

* Refer to NCI CTC Version 2.0.

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

Adverse Event Regardless of Causality[a] (%)	**Fully Supplemented Patients**	**Never Supplemented Patients**
	(N=168)	(N=32)
Neutropenia	24	38
Thrombocytopenia	5	9
Nausea	12	31
Vomiting	11	34
Anorexia	2	9
Diarrhea without colostomy	4	9
Dehydration	4	9
Fever	0	6
Febrile neutropenia	1	9
Infection with Grade 3/4 neutropenia	1	6
Fatigue	17	25

[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%).

For fully supplemented patients treated with ALIMTA plus cisplatin, the incidence of CTC Grade 3/4 fatigue, leukopenia, neutropenia, and thrombocytopenia were greater in patients 65 years or older as compared to patients younger than 65. 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%).

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.

DOSAGE AND ADMINISTRATION
ALIMTA is for Intravenous Infusion Only

Combination Use With Cisplatin

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 hydration consistent with local practice prior to and/or after receiving cisplatin. See cisplatin package insert for more information.

Premedication Regimen

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.

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 μg, and the dose of vitamin B_{12} was 1000 μg. The most commonly used dose of oral folic acid in clinical trials was 400 μg (*see* **WARNINGS**).

Laboratory Monitoring and Dose Reduction 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.

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 5-7.

Table 5: Dose Reduction for ALIMTA 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 regardless of nadir ANC.	50% of previous dose (both drugs).

If patients develop nonhematologic toxicities (excluding neurotoxicity) ≥Grade 3 (except Grade 3 transaminase elevations), ALIMTA 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 6.

Table 6: Dose Reduction - 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	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.
[c] Except Grade 3 transaminase elevation.

In the event of neurotoxicity, the recommended dose adjustments for ALIMTA and cisplatin are described in Table 7. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is experienced.

Table 7: Dose Reduction for ALIMTA 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

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.

Elderly Patients — No dose reductions other than those recommended for all patients are necessary for patients ≥ 65 years of age.

Children — ALIMTA is not recommended for use in children, as safety and efficacy have not been established in children.

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. 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:

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

$$\text{Females: Estimated creatinine clearance for males} \times 0.85$$

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

Hepatically Impaired Patients — ALIMTA is not extensively metabolized by the liver. Dose adjustments based on hepatic impairment experienced during treatment with ALIMTA are provided in Table 6 (*see* **Patients with Hepatic Impairment** *under* **PRECAUTIONS**).

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.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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.

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 and the number of ALIMTA vials needed. Each vial contains 500 mg of ALIMTA. The vial contains an excess of ALIMTA to facilitate delivery of label amount.
3. Reconstitute 500-mg vials with 20 mL of 0.9% Sodium Chloride Injection (preservative free) to give 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. If particulate matter is observed, do not administer.
5. The appropriate volume of reconstituted ALIMTA solution should be further diluted to 100 mL with 0.9% Sodium Chloride Injection (preservative free) and 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.

HOW SUPPLIED

ALIMTA®, pemetrexed for injection is available in sterile single-use vials containing 500 mg pemetrexed.

NDC 0002-7623-01 (VL7623): single-use vial with flip-off cap individually packaged in a carton.

Storage

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.

REFERENCES

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