CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-462

Medical Review(s)

Division Director's Memorandum

Date: February 4, 2004
NDA: 21-462
Sponsor: Eli Lilly and Company
Proprietary Name: Alimta® (pemetrexed for injection)

Administrative History
On July 8, 1992, the initial IND was submitted. The product received Orphan designation on August 28, 2001. On June 10, 2002, this application received Fast Track designation for malignant pleural mesothelioma and the Division accepted Lilly's plan for a rolling submission. The first parts of the NDA were submitted October 24, 2002 and the last reviewable unit (CMC) was received on September 30, 2003. The PDUFA goal date for this priority review is March 30, 2004.

Proposed Indication
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.

Available Therapies
No drug treatment has been shown to prolong survival in this setting.

Clinical Review (see reviews by Dr. White, Dr. Hazarika, and Dr. Johnson)
A single randomized clinical trial was conducted, entitled, "A Single-blind Randomized Phase 3 Trial of Alimta plus Cisplatin versus Cisplatin Alone in Patients with Malignant Pleural Mesothelioma."

This multi-center study included 88 principal investigators at a total of 88 study centers located in 20 countries. The primary objective was to compare survival in chemonaive patients with malignant pleural mesothelioma treated with Alimta plus cisplatin combination therapy to survival in the same patient population treated with cisplatin alone.

A total of 574 patients were entered into the study (signed the informed consent document). Four hundred fifty-six of these patients were randomized to a treatment arm and 448 were treated and constitute the randomized and treated (RT) population.

During this study, after about 25% of the randomized population had been treated, vitamin B_{12} and folic acid supplementation was found to reduce Alimta toxicities. At that time all patients in both treatment groups in the randomized trial were supplemented with vitamins. This resulted in three subgroups in each treatment arm regarding vitamin supplementation. These groups are never supplemented (NS), partially supplemented (PS) and fully

supplemented (FS). Patient totals for the Alimta/cisplatin group are RT 226, FS 168, PS or never supplemented 58, and for the cisplatin alone group are RT 222, FS 163 and PS or NS 59. The FDA review focuses on all RT patients (the primary analysis) and the FS patients (the proposed labeled administration.)

The primary efficacy analysis was comparison of survival between the study arms in the RT population. Differences were assessed using a two-sided log rank test. Because an interim analysis was conducted (resulting in a decision to continue the trial to planned completion), the comparison of survival was tested at the p=0.0476 level.

In the RT patient analysis, the combination of Alimta and cisplatin demonstrated a statistically significant improvement in survival with median survivals of 12.1 versus 9.3 months, respectively (p=0.020). This superiority in the combination arm was also demonstrated in the fully supplemented subgroup with median survivals of 13.3 and 10.0 months in the combination and cisplatin alone groups, respectively (p=0.051). In an exploratory analysis, the effect on survival was larger in females (n=83, 15.7 vs. 7.5 months median survival) than in males (n=305, 11 months vs. 9.4 months).

Pathologic diagnosis of malignant pleural mesothelioma may be difficult. Because of concern that some patients may have other kinds of cancer, a subgroup survival analysis was performed, including only the 303 patients with a histologic diagnosis of malignant pleural mesothelioma confirmed by a central independent pathology review. This subgroup analysis corroborates the primary survival analysis. The median survival times were 13 and 10.2 months in the RT combination and cisplatin alone groups, respectively (p=0.06). The median survival times were 14.4 and 10.3 months in the RT fully supplemented combination and cisplatin alone groups, respectively (p=0.058).

Prior to the trial's initiation, the FDA indicated to the Applicant that tumor response in this disease cannot be reliably assessed and that the FDA would not form primary efficacy decisions based on tumor response or time-to-tumor progression. Tumor response and time-to-progression were assessed, but the results were not interpretable. Tumor response criteria are not well established in pleural malignant mesothelioma. The tumor often grows in sheets rather than well demarcated spherical configurations. The tumor response assessments were inconsistent between the study investigators and the two independent reviewers. The FDA review of the submitted films could confirm tumor response in only 47 of the 94 patients in the combination group for whom the Applicant claimed responses. Patients in the combination group did appear to have a better response rate and longer time-to-progression; however, numerical results for tumor response and time-to-progression are not included in the product label.

Patients were assessed with the Lung Cancer Symptom Scale (LCSS). Although there were statistically significant changes favoring the combination group in some components and in the overall score, none of the changes was judged to be clinically important. No claims regarding the LCSS were included in the label.

Patients were also assessed during the study for pulmonary function by measuring slow vital capacity, forced vital capacity and forced expiratory volume in one second. There were

statistically significant changes in the pulmonary function tests favoring the combination group. However, consultation from the FDA's Division of Pulmonary Drug Products indicated that the reported mean changes were within the range of normal variation of the tests and are not considered clinically important.

The Division of Pulmonary Drugs recommended forced vital capacity (FVC) as the most appropriate pulmonary function test in these patients because the disease effect is constrictive rather than obstructive. To further assess the effect of treatment on pulmonary function, the Oncology Drug Products Division performed the following two analyses intended to consider meaningful changes in pulmonary function using the electronic database.

In the first analysis 337/448 (75%) of RT patients who had a baseline and at least one follow-up FVC, 26.6% and 21.3% of combination group patients had an increase over baseline FVC of $\geq$ 400 mL and $\geq$ 500 mL, respectively, on at least one follow-up visit. The differences between the combination and cisplatin alone groups are statistically significant. However, the increases in FVC were maintained for at least 6 weeks in only about half of the combination group patients. The difference between treatment groups was no longer statistically significant.

In the second analysis 28.4% and 17.2% of combination group patients had an increase from baseline FVC of $\geq$ 20% and $\geq$ 30% on at least one follow-up visit, respectively. The differences between the combination and cisplatin alone treatment groups are statistically significant. The increases in FVC were maintained for at least 6 weeks in only about half of the combination group patients. But the difference between treatment groups remains statistically significant.

Based on these two analyses, together with the overall mean increase, a labeling claim for a modest beneficial effect on pulmonary function can be made.

The adverse effects of the combination regimen are acceptable for chemotherapy drug products. The principal adverse effects that are greater with the combination than with cisplatin alone are myelosuppression, severe nausea and vomiting, and rash/desquamation. Patients in both groups were fatigued and had dyspnea and chest pain, probably related to the underlying disease. Severe hematologic and gastrointestinal adverse effects are significantly reduced by supplementation with vitamin B_{12} and folic acid without any decrement in efficacy.

Alimta is eliminated primarily by the renal route. In clinical studies, patients with creatinine clearance $\geq$ 45 mL/min required no dose adjustments other than those recommended for all patients, although AUC's were increased by about 50-60% in patients with CLcr of 45-50 mL/min. Insufficient patient numbers with creatinine clearance below 45 mL/min have been treated to make dosage recommendations for this patient group. Alimta should not be administered to patients whose creatinine clearance is < 45 mL/min using the Cockcroft and Gault formula or GFR measured by Tc99m-DPTA serum clearance method.

Biostatistical Review (see Dr. Wang's review)
The results of the biostatistical review are presented in the table below and have been previously discussed in the clinical section.

Primary Endpoint: Survival for RT Population (FDA Analysis)

	RT Population (N=448)		FS Population (N=331)		PS+NS Population (N=117)	
	Combo (N=226) n (%)	Cis (N=222) n (%)	Combo (N=168) n (%)	Cis (N=163) n (%)	Combo (N=58) n (%)	Cis (N=59) n (%)
Patients dead[a]	145 (64)	159 (72)	95 (57)	103 (63)	50 (86)	56 (95)
Survival time (months)						
Median	12.1	9.3	13.3	10.0	9.5	7.2
(95% CI)	(10.0,14.4)	(7.8, 10.7)	(11.4,14.9)	(8.4, 11.9)	(8.1, 10.8)	(6.5, 9.9)
p-value[b]						
Long-rank	0.021		0.051		0.253	
Wilcoxon	0.028		0.039		0.440	
Hazard Ratio[c]	0.766		0.758		0.798	
95% CI for Hazard Ratio[c]	(0.61, 0.96)		(0.57, 1.0)		(0.54, 1.17)	

Results based on the analysis of data sets provided by the sponsor.
Combo = combination of cisplatin plus Alimta; Cis = single-agent cisplatin
[a] Patients were died for different reasons: study disease related, study toxicity, and other causes.
[b] P-value is based on the test results for the two treatment groups.
[c] Hazard Ratio is based on the proportional-hazards model with the treatment as single independent variable.

Chemistry/Manufacturing and Controls Review (see Dr. Liang's review for details)
ALIMTA, pemetrexed (L-Glutamic acid, *N*-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-,disodium salt heptahydrate) drug substance, contains one chiral center and is a disodium salt containing seven water molecules of hydration (heptahydrate) in the solid state of the drug product. The molecular formula is $C_{20}H_{19}N_5O_6Na_2.7H_2O$, and the molecular weight is 597.49 daltons.

Pemetrexed drug substance is —— and its structure is well characterized. During the review process, several discrepancies related to stereoisomer control and correct USAN nomenclature were resolved.

Alimta drug product is supplied in glass vials as a single-use sterile lyophilized powder for intravenous infusion. Each —— of Alimta contains —— pemetrexed disodium heptahydrate (equivalent to 500 mg pemetrexed free acid) and 500 mg of mannitol. Sodium hydroxide and, if necessary, hydrochloric acid are added to adjust the pH. Eli Lilly manufactures the drug product in Fegersheim, France.

Each vial of Alimta is reconstituted with 20 mL of commercially available 0.9% Sodium Chloride Injection without preservatives to a concentration of 25 mg/mL of pemetrexed as free acid. This reconstituted pemetrexed solution must be further diluted to 100 mL with

0.9% Sodium Chloride Injection prior to intravenous infusion. The final concentration of drug product solution to be administrated is 0.25 mg/mL pemetrexed as free acid.

During the review process, deficiencies related to the control of drug product total impurities were resolved. The applicant agreed to restrict the limit for total impurities from NMT — % to NMT — % as an interim specification and to reevaluate the limit for total impurities within 24 months (or after ten commercial batches of drug product have been manufactured).

raise clinical concern. Any impurity profile — within the specified — range will be within current impurity limits.

The drug substance, drug product, and the reconstituted drug product solution have adequate stability characteristics to support a 24-month shelf life for the drug product based on primary and supportive stability data.

Nonclinical Review (see Dr. Lee Ham's review and Dr. Morse's team leader memo) Alimta® (pemetrexed disodium) is a pyrrolopyrimidine antifolate. Although it's mechanism of action is not fully understood, multiple non-clinical studies suggest pemetrexed exerts antineoplastic activity by interfering with folate-dependent metabolic processes essential for cell replication. After entrance into the cell (via reduced folate carrier [RFC] and membrane folate-binding protein [FBP]), pemetrexed is rapidly polyglutamated by folypolyglutamate synthetase. Both parent and polyglutamated pemetrexed act as competitive inhibitors of several folate-dependent enzymes, including thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide transferase (GARFT), which are key enzymes for de novo nucleotide biosynthesis. These actions are similar to methotrexate, which has inhibitory effects on thymidylate synthase (TS) and dihydrofolate reductase (DHFR).

When tested in a series of *in vitro* and *in vivo* (xenograft) models of cancer, pemetrexed demonstrated activity against a variety of tumor types, including leukemia (CCRF-CEM, L1210), lung (A549), mesothelioma (NCI-H2052 and MSTO-211H), breast (MCF7), colon (GC3 and HCT8), and ovarian cancer (SKOV1).

Non-clinical toxicity studies were conducted to determine the acute and repeat-dose effects when administered to mice, rats, and dogs. Toxicity studies included: single and repeat dose studies of 2- and 6-weeks intraperitoneal (ip) dosing in mice, and 4- and 6-weeks, and 6-months intravenous (iv) dosing in dogs. In single dose studies, pemetrexed demonstrated limited acute toxicity in mice and rats, but more extensive toxicity in dogs. Six week repeat dose studies were conducted using daily, twice weekly or weekly ip doses in mice and iv doses in dogs. Mice tolerated weekly ip doses of up to 944 mg/m^2 (twice the clinical dose) without death or toxicity, whereas weekly iv dosing at 2099 mg/m^2 (four times the clinical

dose) resulted in the early termination of several dogs. Repeat-dose adverse effects at higher doses caused decreased food consumption, emesis, diarrhea, mucositis, decreased red cell parameters, leukopenia, neutropenia, and increased hepatic enzymes in dogs. In mice, weight loss and leukopenia were the predominant drug toxicities. Histopathologic indices generally occurred in the thymus, lymph nodes, GI tract, testis, bone marrow, and skin.

Pemetrexed (intravenous) doses of ≥ 0.3 mg/m^2 caused testicular atrophy and reduced fertility. Further, pemetrexed was embryotoxic and teratogenic in mice when administered at 0.6 mg/m^2. Pemetrexed caused no genetic damage in a standard battery of *in vitro* tests, mutation and clastogenicity assays, although, pemetrexed was clastogenic in the micronucleus assay. Carcinogenicity studies of pemetrexed disodium have not been conducted.

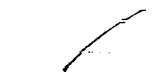
Limited non-clinical investigations of "rescuing agents" (leucovorin and thymidine) were conducted with pemetrexed administration. Results suggest that the co-administration of leucovorin (20 mg/kg im days 5-10; 25 mg/kg im days 4, & 5, and 50 mg/kg iv day 4) reduced or reversed the toxicity of pemetrexed (50 mg/kg iv days 1 & 4) in dogs. Dogs given pemetrexed (50 mg/kg, iv days 0 & 3) with thymidine (8 mg/kg, days 4-7, administration as a continuous infusion) had no toxic alterations associated with pemetrexed compared to the saline-treated controls.

AUC values for pemetrexed were approximately dose proportional following single ip or iv administration to mice, and iv administration to dogs and humans. Elimination half-life was significantly shorter in dogs and man when compared to mice. The PK profile was biphasic following radiocarbon tracer administration, with rapid tissue distribution following an iv dose and subsequent elimination (tissue levels generally did not persist beyond 3 hrs post-dose).

<u>Clinical Pharmacology and Biopharmaceutic Review</u> (see Dr. Booth's review)
The pharmacokinetics of Alimta follow a 2-compartment model, and excretion is predominantly renal. Alimta was not metabolized by any cytochrome P-450, nor did it inhibit any cytochrome P-450 isozyme. Total systemic clearance is 91.8 mL/min and is correlated with glomerular filtration rate and creatinine clearance (CLcr) (Cockcroft-Gault formula). The elimination half-life is 3.5 hours; accumulation was not noted. The pharmacokinetics were unaffected by sex, age or ethnicity.

Cisplatin co-administration did not alter the Alimta's pharmacokinetics or vice versa. Co-administration of carboplatin did not alter the pharmacokinetics of Alimta, but the pharmacokinetics of carboplatin may have been affected. Neither folic acid/vitamin B_{12} nor aspirin (1.3 mg/day) altered Alimta pharmacokinetics. However, ibuprofen increased Alimta AUC by approximately 20% at a moderate dose of 1.6 gm/day. Renal impairment studies of Alimta as a single agent indicated that the Alimta AUC increased by 130% in patients with moderate renal impairment (CLcr 30-50 mL/min; n=6), suggesting that neutropenia might be exacerbated in these patients. These studies were not considered sufficient to provide dosing recommendations for patients with CLcr < 45 mL/min.

Labeling (see DMETS review)
DMETS reviewed the draft container labels, carton, and insert labeling for Alimta and focused on safety issues relating to possible medication errors. DMETS recommended the following changes to minimize potential user errors.

- Carton labeling (500 mg Single-Use Vial): Increase the prominence of the route of administration on the principal display panel by bolding or other means. Repeat the statement, "Caution: Cytotoxic Agent" on the principal display panel.
- 

Data Integrity Issues (see Dr. Gan's Clinical Inspection Summary)
The Division of Scientific Investigation investigated four sites (University of Chicago Hospital, Chicago, IL; Texas Oncology, Dallas, TX; and sites in Milano, Italy and Hamburg, Germany) and found the data adequate for safety and efficacy evaluation.

Tradename consultation
The tradename, Alimta, is acceptable to DDMAC and DMETS (see DMETS review).

Pediatric Considerations
Malignant pleural mesothelioma does not occur in children.

Conclusions and Recommendations: **Approval**
The trial contained in this application demonstrates a survival advantage in patients with malignant pleural mesothelioma treated with Alimta plus cisplatin compared to those treated with single-agent cisplatin. These patients were either unresectable or were otherwise not candidates for curative surgery. No other drug, including cisplatin, has demonstrated a survival advantage in this life-threatening disease setting associated with a short survival. The Division has consistently accepted a survival improvement to demonstrate clinical benefit. Hence, this application was not presented to the Oncologic Drugs Advisory Committee (ODAC). The trial's design allows demonstration of Alimta's effect on the primary study endpoint (survival).

Although a single randomized trial supports this NDA, this trial was multi-institutional with over 88 study centers enrolling over 574 patients and is the largest randomized study ever conducted in this disease. The primary efficacy analysis was confirmed in the randomized and treated (RT) population as well as in a subset population--the fully vitamin supplemented group (FS). Although the Division did not allow specific numbers to be included in response rate and time-to-progression analyses because of the inaccuracies and difficulties in

measuring disease in mesothelioma patients, the Division acknowledges that the combination treatment group did appear to show an improvement in these secondary endpoints. An additional secondary endpoint of improvement in pulmonary function (forced vital capacity) was also included in the product label.

The safety profile of the proposed combination of Alimta plus cisplatin with vitamin supplement (and corticosteroids for skin rash prophylaxis) is consistent with other cytotoxic chemotherapy agents approved by the Division. The primary toxicities include myelosuppression, fatigue, nausea, vomiting, and dyspnea. The product label clearly advises physicians of specific vitamin use to reduce the toxicity. Hence, an acceptable risk-benefit relationship is noted with the combination. The recommended regulatory action is approval of NDA 21-462.

Richard Pazdur, MD
Director, Division of Oncology Drug Products

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/s/

Dianne Spillman
2/4/04 12:26:54 PM
CSO

Richard Pazdur
2/4/04 12:31:55 PM
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ONCOLOGY DRUGS CLINICAL TEAM LEADER REVIEW OF NDA

NDA 21462

NAME OF DRUG Alimta (pemetrexed)

APPLICANT Eli Lilly

CLINICAL TEAM LEADER John R. Johnson M. D.

DATE REVIEW COMPLETED December 10, 2003

ADMINISTRATIVE 8-28-01 Orphan Drug Designation
6-10-02 Fast Track Designation
10-24-02 Initial Rolling Submission
9-30-03 Final Rolling Submission

PROPOSED INDICATION

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

PRESENT ARMAMENTARIUM

No treatment has been shown to prolong survival in this setting.

CLINICAL TRIAL

One randomized clinical trial was conducted.

Title:

A Single-blind Randomized Phase 3 Trial of Alimta plus Cisplatin versus Cisplatin Alone in Patients with Malignant Pleural Mesothelioma

This multicenter study included 88 principal investigators who entered patients at a total of 88 study centers located in 20 countries.

Primary Objective:

To compare survival in chemonaive patients with malignant pleural mesothelioma whose disease is either unresectable or who are otherwise not candidates for curative surgery when treated with Alimta plus cisplatin combination therapy to survival in the same patient population when treated with cisplatin alone.

Secondary Objectives:

To compare between the two treatment arms: (1) time-to-event efficacy measures, including: a) duration of response for responding patients, b) time to progressive disease, c) time to treatment failure; (2) tumor response rate; (3) clinical benefit response rate; (4) Lung Cancer Symptom Scale (LCSS) patient and observer scores; (5) pulmonary function tests; (6) lung density; (7) relative toxicities; (8) to assess the impact of folic acid and vitamin B12 supplementation on toxicity; (9) pharmacokinetic effects; (10) information regarding vitamin metabolite status in this patient population.

Treatment:

Alimta plus cisplatin treatment arm: Alimta was administered at a dose of 500 mg/m2 diluted in approximately 100 mL normal saline as a 10-minute intravenous infusion. Approximately 30 minutes after the administration of Alimta, cisplatin was administered at a dose of 75 mg/m2 over 2 hours. Both drugs were administered on Day 1 of a 21-day period. This 21-day period defined one cycle of therapy.

Cisplatin alone treatment arm: Approximately 100 mL normal saline was given as an intravenous infusion over approximately 10 minutes. Approximately 30 minutes after the administration of normal saline, cisplatin was administered at 75 mg/m2 over 2 hours on Day 1 of a 21-day period. This 21-day period defined one cycle of therapy.

Both treatment arms:

Dexamethasone 4 mg (or an equivalent corticosteroid) was taken by all patients orally twice a day 1 day before, on the day of, and 1 day after each dose of Alimta for primary prophylaxis against rash.

Folic acid and vitamin B12 for supplementation were standard components of therapy for all patients participating in the study from December 2, 1999 onwards. Folic acid 350 to 1000 µg was administered orally daily, beginning approximately 1 to 3 weeks before the first dose of therapy and continued daily for 1 to 3 weeks after the patient discontinued treatment. A vitamin B12 injection 1000 µg was administered intramuscularly approximately 1 to 3 weeks before the first dose of therapy and was repeated approximately every 9 weeks until the patient discontinued study therapy.

Patient Population:

A total of 574 patients were entered into the study (that is,signed the Informed Consent Document). Four hundred fifty six of these patients were randomized to a treatment arm and 448 of these patients were treated and constitute the randomized and treated (RT) population.

Initially no vitamin supplementation was given. Part way through the study it became apparent from other Alimta studies that vitamin supplementation was beneficial from a safety standpoint. At that time all patients in both treatment groups in the randomized trial were supplemented with vitamins. This resulted in three subgroups in each treatment arm regarding vitamin supplementation. These groups are never supplemented (NS), partially supplemented (PS) and fully supplemented (FS). Results are reported for each group. This review will focus on all RT patients (the primary analysis) and the FS patients (the proposed labeled administration.)

Alimta plus cisplatin: Total RT 226, Male 184, Female 42,
Fully Supplemented (FS) 168, Partially Supplemented (PS) or
Never Supplemented (NS) 58.

Cisplatin alone: Total RT 222, Male 181, Female 41,
Fully Supplemented (FS) 163, Partially Supplemented (PS) or
Never Supplemented (NS) 59.

Statistics:

The primary efficacy analysis was comparison of survival time between the study arms in the RT population. Differences were assessed using a two-sided log rank test. Because an interim analysis was conducted (resulting in a decision to continue the trial to planned completion), the comparison of survival was tested at the p=0.0476 level.

Patient Characteristics:

The following Tables compiled by the Applicant show the disease and demographic factors for the study patients. These are well balanced between the treatment groups.

Table JMCH.11.3. Summary of Patient Characteristics RT Population by Supplementation Status H3E-MC-JMCH

	LY/cis		Cisplatin	
	FS (N=168)	PS+NS (N=58)	FS (N=163)	PS+NS (N=59)
Sex				
Male	136 (81.0%)	48 (82.8%)	134 (82.2%)	47 (79.7%)
Female	32 (19.0)	10 (17.2)	29 (17.8)	12 (20.3)
Origin				
Caucasian	150 (89.3)	54 (93.1)	153 (93.9)	53 (89.8)
Hispanic	10 (6.0)	1 (1.7)	7 (4.3)	5 (8.5)
Asian[1]	7 (4.2)	3 (5.2)	3 (1.8)	1 (0.7)
African	1 (0.6)	0	0	0
Age				
Median	60	62	60	61
Minimum	29	32	19	35
Maximum	85	77	82	84

1 Western and East/Southeast Asian have been combined.

Table JMCH.11.5. Baseline Stratification Factors Used for Randomization RT Population by Supplementation Status H3E-MC-JMCH

	LY/cis		Cisplatin	
	FS (N=168)	PS+NS (N=58)	FS (N=163)	PS+NS (N=59)
KPS				
Low (≤80)	83 (49.4%)	26 (44.8)	69 (42.3%)	28 (47.5)
High (≥90)	85 (50.6)	32 (55.2)	94 (57.7)	31 (52.5)
Degree of Measurability[1]				
Unidimensional	61 (36.5)	12 (20.7)	62 (38.0)	11 (18.6)
Bidimensional	106 (63.5)	46 (79.3)	101 (62.0)	48 (81.4)
Histologic Subtype				
Epithelial	117 (69.6)	37 (63.8)	113 (69.3)	39 (66.1)
Mixed	25 (14.9)	12 (20.7)	25 (15.3)	11 (18.6)
Sarcomatoid	14 (8.3)	4 (6.9)	17 (10.4)	8 (13.6)
Other	12 (7.1)	5 (8.6)	8 (4.9)	1 (1.7)
WBC				
Low (<8.3 Gl/L)	72 (42.9)	25 (43.1)	68 (41.7)	23 (39.0)
High (≥8.3 Gl/L)	96 (57.1)	33 (56.9)	95 (58.3)	36 (61.0)
Pain Intensity[2]				
Low (<20 mm)	82 (49.4)	30 (51.7)	80 (49.1)	33 (55.9)
High (≥20 mm)	84 (50.6)	28 (48.3)	83 (50.9)	26 (44.1)
Analgesic Consumption				
Low (<60 mg morp eq/day)	129 (76.8)	44 (75.9)	124 (76.1)	46 (78.0)
High (≥60 mg morp eq/day)	39 (23.2)	14 (24.1)	39 (23.9)	13 (22.0)
Dyspnea[2]				
Low (<20 mm)	66 (39.8)	25 (43.1)	68 (41.7)	24 (40.7)
High (≥20 mm)	100 (60.2)	33 (56.9)	95 (58.3)	35 (59.3)
Homocysteine				
Low (<12 umol/L)	119 (70.8)	36 (62.1)	118 (72.4)	38 (64.4)
High (≥12 umol/L)	49 (29.2)	22 (37.9)	45 (27.6)	21 (35.6)
Sex				
Male	136 (81.0)	48 (82.8)	134 (82.2)	47 (79.7)
Female	32 (19.0)	10 (17.2)	29 (17.8)	12 (20.3)

1 A single patient was missing their evaluable disease measurement at baseline.

2 Patients 302-3025 and 720-7209 completed the patient LCSS at baseline, but outside of the protocol defined window, those data are not included in the reporting database.

Table JMCH.11.7. Summary of Baseline Disease Characteristics RT Population by Supplementation Status H3E-MC-JMCH

	LY/cis		Cisplatin	
	FS (N=168)	PS+NS (N=58)	FS (N=163)	PS+NS (N=59)
Diagnosis / Histology				
Epithelial	117 (69.6%)	37 (63.8%)	113 (69.3%)	39 (66.1%)
Mixed	25 (14.9)	12 (20.7)	25 (15.3)	11 (18.6)
Sarcomatoid	14 (8.3)	4 (6.9)	17 (10.4)	8 (13.6)
Other	12 (7.1)	5 (8.6)	8 (4.9)	1 (1.7)
Stage at Entry				
Ia	8 (4.8)	1 (1.7)	7 (4.3)	1 (1.7)
Ib	7 (4.2)	0	5 (3.1)	1 (1.7)
II	27 (16.2)	8 (13.8)	27 (16.8)	6 (10.2)
III	51 (30.5)	22 (37.9)	49 (30.4)	19 (32.2)
IV	74 (44.3)	27 (46.6)	73 (45.3)	32 (54.2)
Unspecified	1 (0.6)	0	2 (1.2)	0
Performance Status				
70	25 (14.9)	12 (20.7)	22 (13.5)	9 (15.3)
80	58 (34.5)	14 (24.1)	47 (28.8)	19 (32.2)
90	67 (39.9)	26 (44.8)	69 (42.3)	25 (42.4)
100	18 (10.7)	6 (10.3)	25 (15.3)	6 (10.2)

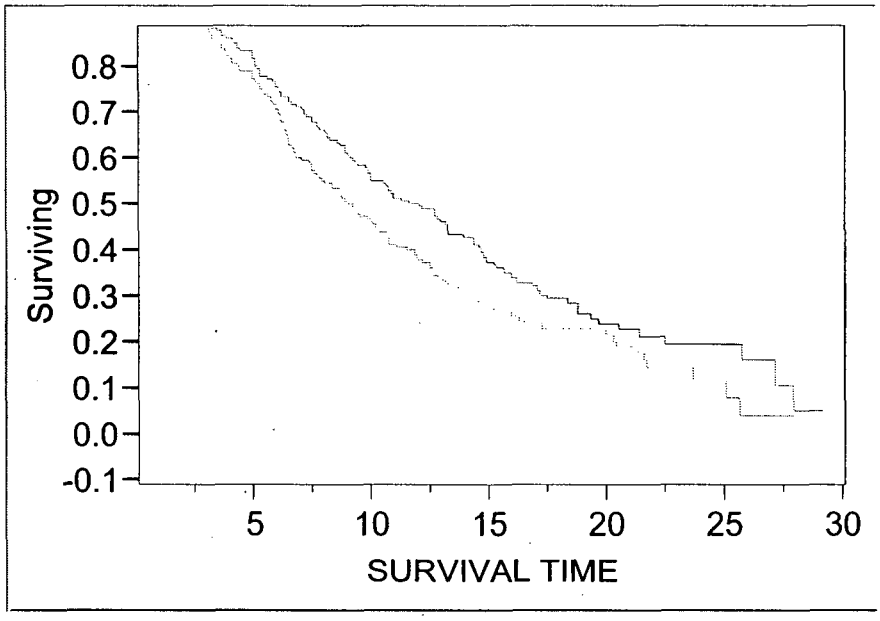
Efficacy Results:

Survival

In the all RT patients analysis the combination of Alimta and cisplatin demonstrates a statistically significant improvement in survival compared to cisplatin alone with median survivals of 12.1 versus 9.3 months, respectively (p=0.020). An ITT analysis on all randomized patients, including 8 patients not in the RT analysis, yields nearly identical results to the RT analysis. This superiority in the Alimta/cisplatin arm is also demonstrated in the fully supplemented subgroup with median survivals of 13.3 and 10.0 months in the Alimta/cisplatin and cisplatin alone treatment groups, respectively (p=0.051).

All Randomized Treated Patients (448)

Product-Limit Survival Fit
Survival Plot



Time intervals are in months.

M2 = Alimta/cisplatin (upper curve)
M39 = cispaltin alone (lower curve)

Summary

Group	N Failed	N Censored	Mean	Std Dev
M2	145	81	13.5305 Biased	0.64943
M39	159	63	11.485 Biased	0.56377
Combined	304	144	12.5648 Biased	0.44228

Quantiles

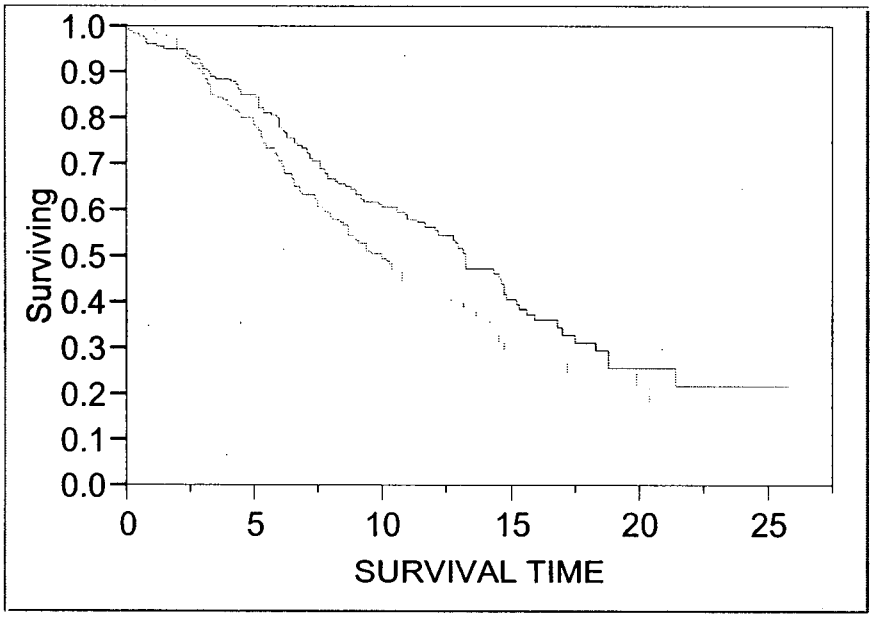
Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
M2	12.1	10	14	6.1	19.7
M39	9.3	7.8	10.7	5.5	16.4
Combined	10.4	9.3	11.9	5.9	18.9

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	5.4033	1	0.0201
Wilcoxon	4.8458	1	0.0277

RT Fully Supplemented Patients (331)

Product-Limit Survival Fit
Survival Plot



Time intervals are in months.

M2 = Alimta/cisplatin (upper curve)
M39 = cispaltin alone (lower curve)

Summary

Group	N Failed	N Censored	Mean	Std Dev
M2	95	73	12.8946 Biased	0.57646
M39	103	60	11.1832 Biased	0.55631
Combined	198	133	12.1377 Biased	0.41116

Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
M2	13.3	11.4	14.9	6.6	21.5
M39	10	8.4	11.9	5.4	17.3
Combined	11.9	10	13.3	6	18.9

Tests Between Groups

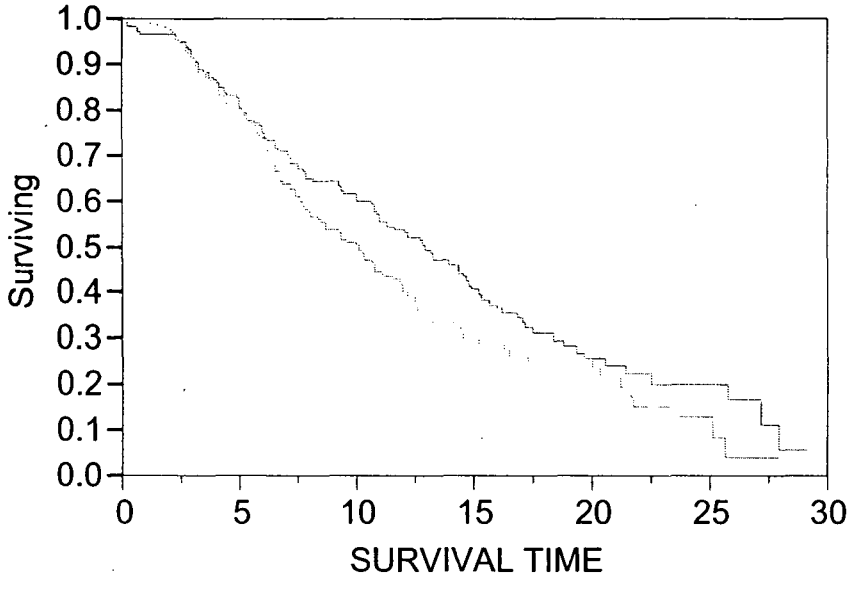
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	3.8084	1	0.0510
Wilcoxon	4.2649	1	0.0389

Pathologic diagnosis of malignant pleural mesothelioma is sometimes difficult. Because of concern that some patients may have other kinds of cancer a subgroup analysis of survival was done including only patients with a histologic diagnosis of malignant pleural mesothelioma confirmed by central independent pathology review. This subgroup

analysis supports the primary survival analysis. The median survival times were 13 and 10.2 months in the RT Alimta/cisplatin and cisplatin alone treatment groups, respectively (p=0.06). The median survival times were 14.4 and 10.3 months in the RT fully supplemented Alimta/cisplatin and cisplatin alone treatment groups, respectively (p=0.058).

Confirmed Mesothelioma Diagnosis
All RT Patients (303)

Product-Limit Survival Fit
Survival Plot



Time intervals are in months.

M2 = Alimta/cisplatin (upper curve)
M39 = cispaltin alone (lower curve)

Summary

Group	N Failed	N Censored	Mean	Std Dev
M2	101	52	13.9642 Biased	0.76937
M39	107	43	12.0324 Biased	0.68229
Combined	208	95	13.0605 Biased	0.52762

Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
M2	13	10.8	14.8	6.1	20.6
M39	10.2	8	12	5.9	20
Combined	11.1	10.1	12.9	6	20

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	3.3892	1	0.0656
Wilcoxon	2.6854	1	0.1013

Tumor Response and Time to Tumor Progression

Tumor response and time to progression were assessed, but the results were not satisfactory. Tumor response criteria are not well established in pleural malignant mesothelioma where the tumor often grows in sheets rather than more spherical configurations. As shown below, the tumor response assessments were not consistent between the study Investigators and the two Independent reviewers. In addition FDA review of the submitted films could confirm the tumor response in only 47 of the 94 patients in the Alimta/cisplatin treatment group for whom the Applicant claimed a tumor response. Thus the FDA does not believe it is appropriate to include numerical results for tumor response and time to progression in the labeling. It did appear that there is a better tumor response rate and longer time-to-tumor progression in the Alimta/cisplatin group.

Prior to start of the study the FDA indicated to the Applicant that tumor response in this disease can not be reliably assessed and that the FDA would not make any important decisions regarding efficacy based on tumor response or time to tumor progression.

Tumor response was assessed by the study Investigators and by two Independent reviewers. The protocol specified primary result was the assessment by the Independent reviewers. If the two Independent reviewers disagreed, a third Independent reviewer broke the tie. The Independent reviewers did not assess progression.

LILLY
ALIMTA RESPONSES
N=226

Investigator		94
	Independent #1	60
	Independent #2	71
	Independent	68
Independent #1		72
	Independent #2	66
	Investigator	61
Independent #2		88
	Independent #1	66
	Investigator	71
Independent		84
Independent #1 and #2 Disagree		28
Independent #3 Resp		21of 28
FDA		47

LILLY
CISPLATIN RESPONSES
N=222

Investigator		37
Independent #1	20	
Independent #2	24	
Independent	23	
Independent #1		27
Independent #2	23	
Investigator	20	
Independent #2		38
Independent #1	23	
Investigator	24	
Independent		30
Independent #1 and #2 Disagree		19
Independent #3 Resp		9 of 19
FDA		Not Done

Lung Cancer Symptom Scale

Patients were assessed during the study using the Lung Cancer Symptom Scale (LCSS). Although there were statistically significant changes favoring the Alimta/cisplatin treatment group in some of the components and in the overall score, none of the changes were clinically important.

Pulmonary Function Studies

Patients were assessed with FVC, SVC and FEV1. The FDA Division of Pulmonary Drug Products recommends FVC as the most appropriate test of pulmonary function in this patient population because their main impairment is constrictive rather than obstructive.

The Applicant's analysis compares the average change from baseline in RT patients in each treatment group. The average change in FVC from baseline is + 110 ml for the Alimta/cisplatin group and - 50 ml for the cisplatin alone group. This difference is statistically significant ($p=0.001$), but it falls within the normal variation of the test (200 ml) per the American Thoracic Society and is not considered clinically important, per the recommendation of the FDA Division of Pulmonary Drug Products.

To further assess the effect of treatment on pulmonary function this reviewer employed the electronic database to determine the proportions of patients in each treatment group having an increase from baseline in FVC of $\geq$ 400 ml and $\geq$ 500 ml on at least one follow-up visit and on at least two follow-up visits. Follow-up visits were six weeks apart. A second similar analysis determined the proportions of patients in each treatment group having an increase from baseline in FVC of $\geq$ 20% and $\geq$ 30% on at least one follow-up visit and at least two follow-up visits.

In the 337/448 (75%) of RT patients who had a baseline and at least one follow-up FVC, 26.6% and 21.3% of Alimta/cisplatin group patients had an increase over baseline FVC of $\geq$ 400 ml and $\geq$ 500 ml on at least one follow-up visit, respectively. The differences between the Alimta/cisplatin and cisplatin alone treatment groups are statistically significant. However, the increases in FVC were maintained for at least 6 weeks in only about half of the Alimta/cisplatin group patients. The difference between treatment groups was no longer statistically significant.

In the second analysis 28.4% and 17.2% of Alimta/cisplatin group patients had an increase from baseline FVC of $\geq$ 20% and $\geq$ 30% on at least one follow-up visit, respectively. The differences between the Alimta/cisplatin and cisplatin alone treatment groups are statistically significant. The increases in FVC were maintained for at least 6 weeks in only about half of the Alimta/cisplatin group patients. But the difference between treatment groups remains statistically significant. Based on the results of these

two analyses, a claim for a modest beneficial effect on pulmonary function (FVC) can be made in the label.

The results are presented in the following Tables.

FVC Increase from Baseline
All Patients with Baseline and at
Least One Follow-up FVC
N=337

	Alimta/Cisplatin N=169	Cisplatin alone N=168	P Value *
Increase ≥ 400 ml ≥ 1 Visit	26.6 %	17.9 %	P=0.03
Increase ≥ 500 ml ≥ 1 Visit	21.3 %	11.9%	P=0.01
Increase ≥ 400 ml ≥ 2 Visits	13.6 %	9.5 %	P=0.19
Increase ≥500 ml ≥ 2 Visits	11.2 %	6.0 %	P=0.09

* P values are Fishers Exact test, two-sided.

FVC Per Cent Increase from Baseline
All Patients with Baseline and at
Least One Follow-up FVC
N=337

	Alimta/Cisplatin N=169	Cisplatin alone N=168	P Value *
Increase ≥ 20% ≥ 1Visit	28.4 %	13.7 %	P=0.001
Increase ≥ 30% ≥ 1 Visit	17.2 %	5.4 %	P=0.0009
Increase ≥ 20% ≥ 2 Visits	14.2 %	7.1 %	P=0.051
Increase 30% ≥ 2 Visits	8.3%	2.4%	P=0.026

* P values are Fishers Exact test, two-sided.

Safety Results:

Adverse events are presented in the following Tables.

Alimta is eliminated primarily by the renal route. 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 or GFR measured by Tc99m-DPTA serum clearance method. Supplementation with vitamin B 12 and folic acid and concomitant treatment with dexamethasone are necessary to decrease adverse effects.

Adverse Events Summary (≥5% Incidence) in RT Population

Adverse Event	Alimta/Cisplatin N=226				Cisplatin N=222			
	All grades		Grade 3/4		All grades		Grade 3/4	
	N	%	N	%	N	%	N	%
Neutrophils/granulocytes	139	61.5	65	28.8	33	14.9	5	2.3
Fatigue	187	82.7	41	18.1	167	75.2	34	15.3
Leukocytes	130	57.5	41	18.1	45	20.3	3	1.4
Nausea	195	86.3	33	14.6	177	79.7	14	6.3
Vomiting	145	64.2	31	13.7	117	52.7	8	3.6
Dyspnea	149	65.9	25	11.1	146	65.8	32	14.4
Hypertension	56	24.8	21	9.3	74	33.3	36	16.2
Chest pain	90	39.8	18	8.0	69	31.1	16	7.2
Hemoglobin	73	32.3	14	6.2	34	15.3	1	0.5
Platelets	66	29.2	13	5.8	19	8.6	0	0.0
Thrombosis/embolism	14	6.2	12	5.3	10	4.5	9	4.1
Diarrhea without colostomy	64	28.3	11	4.9	35	15.8	1	0.5
Tumor pain	42	18.6	11	4.9	37	16.7	12	5.4
Dehydration	20	8.8	10	4.4	2	0.9	2	0.9
Stomatitis/pharyngitis	81	35.8	9	4.0	20	9.0	0	0.0
Anorexia	87	38.5	8	3.5	61	27.5	1	0.5
Constipation	103	45.6	8	3.5	90	40.5	3	1.4
Renal Genitourinary-Other	73	32.3	8	3.5	66	29.7	6	2.7
Constitutional Symptoms-Other	22	9.7	6	2.7	18	8.1	2	0.9
Pleuritic pain	39	17.3	6	2.7	39	17.6	10	4.5
Other pain	33	14.6	5	2.2	46	20.7	7	3.2
Pulmonary-Other	42	18.6	5	2.2	37	16.7	4	1.8
Febrile neutropenia *	4	1.8	4	1.8	0	0.0	0	0.0
Infection with grade 3 or 4 Neutropenia	20	8.8	4	1.8	13	5.9	1	0.5
Infection without Neutropenia	25	11.1	4	1.8	12	5.4	2	0.9
Other Gastrointestinal	44	19.5	4	1.8	30	13.5	1	0.5
Dysphagia, esophagitis, odynophagia	12	5.3	3	1.3	11	5.0	1	0.5
Mood alteration-anxiety agitation	26	11.5	3	1.3	24	10.8	1	0.5
Other endocrine	18	8.0	3	1.3	18	8.1	0	0.0
Rash/desquamation	61	27.0	3	1.3	26	11.7	0	0.0
Abdominal pain or cramping	21	9.3	2	0.9	16	7.2	1	0.5
Edema	34	15.0	2	0.9	33	14.9	5	2.3
Fever	36	15.9	2	0.9	18	8.1	0	0.0
Infection/Febrile Neutropenia-Other *	5	2.2	2	0.9	4	1.8	0	0.0
Inner ear hearing	21	9.3	2	0.9	30	13.5	2	0.9
Mood alteration-depression	28	12.4	2	0.9	21	9.5	3	1.4
Other auditory/hearing	15	6.6	2	0.9	11	5.0	0	0.0

Other musculoskeletal	18	8.0	2	0.9	18	8.1	2	0.9
Alopecia	31	13.7	1	0.4	15	6.8	0	0.0
Cough	90	39.8	1	0.4	82	36.9	2	0.9
Creatinine	39	17.3	1	0.4	26	11.7	2	0.9
Dizziness/lightheadedness	20	8.8	1	0.4	19	8.6	0	0.0
Dyspepsia/heartburn	26	11.5	1	0.4	10	4.5	0	0.0
Headache	29	12.8	1	0.4	24	10.8	1	0.5
Other neurology	18	8.0	1	0.4	13	5.9	1	0.5
SGPT(ALT)	17	7.5	1	0.4	20	9.0	1	0.5
Sweating	29	12.8	1	0.4	27	12.2	0	0.0
Tearing	15	6.6	1	0.4	1	0.5	0	0.0
Weight loss	42	18.6	1	0.4	31	14.0	2	0.9
Insomnia	36	15.9	0	0.0	40	18.0	3	1.4
Neuropathy-sensory	36	15.9	0	0.0	30	13.5	1	0.5
SGOT(AST)	18	8.0	0	0.0	12	5.4	1	0.5
Allergic rhinitis	20	8.8	0	0.0	8	3.6	0	0.0
Conjunctivitis	21	9.3	0	0.0	1	0.5	0	0.0
Other Dermatology/Skin	16	7.1	0	0.0	15	6.8	0	0.0
Other ocular/visual	12	5.3	0	0.0	6	2.7	0	0.0
Taste disturbance	21	9.3	0	0.0	15	6.8	0	0.0
Urinary frequency/urgency	16	7.1	0	0.0	9	4.1	0	0.0

* Included because of importance

Adverse Events Summary (≥ 5% Incidence) in RT Fully Supplemented Population

Adverse Event	Alimta/Cisplatin N=226				Cisplatin N=222			
	All grades		Grade 3/4		All grades		Grade 3/4	
	N	%	N	%	N	%	N	%
Neutrophils/granulocytes	96	57.1	41	24.4	22	13.5	5	3.1
Fatigue	137	81.5	29	17.3	120	73.6	21	12.9
Leukocytes	92	54.8	26	15.5	30	18.4	1	0.6
Nausea	142	84.5	20	11.9	128	78.5	9	5.5
Dyspnea	110	65.5	19	11.3	103	63.2	15	9.2
Hypertension	44	26.2	19	11.3	56	34.4	29	17.8
Vomiting	99	58.9	18	10.7	83	50.9	7	4.3
Chest pain	68	40.5	14	8.3	50	30.7	11	6.7
Hemoglobin	57	33.9	10	6.0	24	14.7	1	0.6
Thrombosis/embolism	12	7.1	10	6.0	6	3.7	6	3.7
Platelets	44	26.2	9	5.4	15	9.2	0	0.0
Tumor pain	31	18.5	8	4.8	24	14.7	7	4.3
Dehydration	12	7.1	7	4.2	2	1.2	2	1.2
Constipation	78	46.4	6	3.6	66	40.5	1	0.6
Diarrhea without colostomy	43	25.6	6	3.6	25	15.3	1	0.6
Other pain	26	15.5	5	3.0	42	25.8	7	4.3
Pulmonary-Other	34	20.2	5	3.0	31	19.0	4	2.5
Renal/Genitourinary-Other	52	31.0	5	3.0	50	30.7	4	2.5
Stomatitis/pharyngitis	47	28.0	5	3.0	13	8.0	0	0.0
Anorexia	59	35.1	4	2.4	44	27.0	1	0.6
Constitutional Symptoms-Other	18	10.7	4	2.4	14	8.6	2	1.2
Infection without Neutropenia	21	12.5	4	2.4	7	4.3	0	0.0
Other Gastrointestinal	33	19.6	3	1.8	26	16.0	1	0.6
Pleuritic pain	29	17.3	3	1.8	31	19.0	8	4.9
Dysphagia, esophagitis, odynophagia	10	6.0	2	1.2	9	5.5	0	0.0
Edema	24	14.3	2	1.2	25	15.3	4	2.5
Hyperglycemia	8	4.8	2	1.2	11	6.7	6	3.7
Infection/Febrile Neutropenia-Other *	5	3.0	2	1.2	3	1.8	0	0.0
Mood alteration-depression	23	13.7	2	1.2	15	9.2	2	1.2
Other cardiovascular/general	19	11.3	2	1.2	19	11.7	3	1.8
Other musculoskeletal	14	8.3	2	1.2	13	8.0	2	1.2
Cough	64	38.1	1	0.6	61	37.4	2	1.2
Creatinine	26	15.5	1	0.6	18	11.0	2	1.2
Dizziness/lightheadedness	16	9.5	1	0.6	16	9.8	0	0.0
Dyspepsia/heartburn	20	11.9	1	0.6	6	3.7	0	0.0
Headache	21	12.5	1	0.6	18	11.0	1	0.6
Infection with grade 3 or 4 Neutropenia	10	6.0	1	0.6	6	3.7	0	0.0
Mood alteration-anxiety/agitation	22	13.1	1	0.6	14	8.6	0	0.0
Other auditory/hearing	11	6.5	1	0.6	8	4.9	0	0.0
Other endocrine	12	7.1	1	0.6	16	9.8	0	0.0
Rash/desquamation	37	22.0	1	0.6	16	9.8	0	0.0
Sweating	24	14.3	1	0.6	17	10.4	0	0.0
Abdominal pain or cramping	13	7.7	0	0.0	13	8.0	1	0.6
Inner ear/hearing	13	7.7	0	0.0	21	12.9	2	1.2
Insomnia	28	16.7	0	0.0	31	19.0	1	0.6
Neuropathy-sensory	29	17.3	0	0.0	24	14.7	1	0.6
Other neurology	14	8.3	0	0.0	11	6.7	1	0.6
SGOT(AST)	14	8.3	0	0.0	10	6.1	1	0.6
SGPT(ALT)	10	6.0	0	0.0	17	10.4	1	0.6
Weight loss	32	19.0	0	0.0	18	11.0	1	0.6

Included because of importance

Grade 3/4 Adverse Events in Fully Supplemented versus Never Supplemented Patients treated with Alimta/Cisplatin

Adverse Events	Fully Supplemented % N=168	Never Supplemented % N=32
Neutrophils/granulocytes	24.4	37.5
Fatigue	17.3	31.3
Leukocytes	15.5	34.4
Nausea	11.9	31.3
Dyspnea	11.3	12.5
Hypertension	11.3	3.1
Vomiting	10.7	34.4
Chest pain	8.3	6.3
Hemoglobin	6.0	9.4
Thrombosis/embolism	6.0	3.1
Platelets	5.4	9.4
Tumor pain	4.8	6.3
Dehydration	4.2	9.4
Constipation	3.6	3.1
Diarrhea without colostomy	3.6	9.4
Febrile neutropenia	0.6	9.4
Infection with Grade3/4 Neutropenia	0.6	6.3

CONCLUSION

Safety and efficacy have been adequately demonstrated.

RECOMMENDATION

This NDA is approvable with labeling revisions. Please see labeling revisions by the FDA Alimta review team.

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/s/

John Johnson
1/24/04 03:00:06 PM
MEDICAL OFFICER

Clinical Review

NDA 21-462

ALIMTA (pemetrexed, MTA, LY231514) for injection

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

Applicant:
Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

Clinical Review Team
CDER, OND, ODE1, Division of Oncology Drug Products
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Documents reviewed: 10/24/2002 (Rolling Submission), 11/22/2002, 11/26/2002, 1/10/2003, 2/13/2003, 3/24/2003 (financial disclosure), 5/9/2003, 5/29/2003, 7/23/2003 (Safety Update), 7/30/2003, 8/8/2003, 8/15/2003, 8/21/2003, 8/28/2003, 9/2/2003, 9/12/2003, 9/15/2003, 9/19/2003, 9/22/2003, 9/29/2003, 10/6/2003 (labeling), 10/20/2003, 11/4/2003 (labeling), 11/6/2003, 11/14/2003 (labeling), 11/14A/2003, 11/18/2003, 11/24/2003 (labeling), 11/26/2003, 12/4/2003 (financial disclosure), 12/4A/2003, 12/5/2003 (labeling), 12/10/2003 (financial disclosure), 12/15A/2003 (labeling), 12/16/2003.

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Clinical Review for NDA 21-462

Executive Summary

I. Recommendations

1. Recommendation on Approvability

One single-blind, randomized, controlled trial, demonstrating the efficacy and safety of Alimta in combination with cisplatin for the treatment of malignant pleural mesothelioma patients whose disease is either unresectable or who are not candidates for curative surgery has been submitted and reviewed. The pivotal trial was multicenter with United States and non-US sites. The combination of Alimta plus cisplatin is the first chemotheraupetic regimen to demonstrate a survival benefit in malignant pleural mesothelioma in comparison to a control regimen.

The overall survival analyses of the randomized and treated (RT) and the intent-to-treat populations demonstrated a statistically significant improvement in survival in favor of the alimta/cisplatin arm compared to cisplatin alone. In the fully folic acid/vitamin B12 supplemented group, the alimta/cisplatin arm was favored and was marginally statistically significant. Sixty-seven percent of the patients enrolled on study had pathologically confirmed mesothelioma; in the confirmed mesothelioma subset, survival analyses of the RT and the fully folic acid/vitamin B12 supplemented groups demonstrated a marginally significant survival advantage in favor of the alimta/cisplatin arm. The under-powered female subgroup demonstrated in RT and the fully folic acid/vitamin B12 supplemented groups a statistically significant survival advantage in favor of the alimta/cisplatin; a similar analysis in the much larger male subgroup demonstrated only trends in favor of the alimta/cisplatin arm[1]. The white subgroup demonstrated, in the RT and the fully folic acid/vitamin B12 supplemented groups, a statistically significant survival advantage in favor of the alimta/cisplatin; the under-powered non-white group demonstrated a trend in favor of alimta/cisplatin in the RT group and trend in favor of cisplatin in the fully folic acid/vitamin B12 supplemented group. The age < 65 years subgroup demonstrated, in the RT and the fully folic acid/vitamin B12 supplemented groups, a survival advantage in favor of the alimta/cisplatin that was statistically significant and marginally significant, respectively. The age $\geq$ 65 years subgroup demonstrated trends in favor of the alimta/cisplatin arm.

Alimta in combination with cisplatin has satisfactorily demonstrated a consistent survival advantage compared to cisplatin alone in patients with pleural malignant mesothelioma in a randomized, single-blinded study.

[1] Lilly did a multifactorial survival analysis considering prognostic factors and there was no gender effect; ISE document submitted 3/24/2003.

The common grade 3 or grade 4 laboratory toxicities in the RT group treated with Alimta plus cisplatin were neutropenia (28.8%), leucopenia (18.1%), thrombocytopenia (5.8%) and anemia (6.2%). In a subgroup analysis of patients fully supplemented with folic acid + vitamine B12 (FS), the Alimta + cisplatin treated arm had neutropenia (24.4%), leucopenia (15.5%), anemia (6%), thrombocytopenia (5.4%) while the cisplatin only arm had neutropenia (3.1%), leucopenia (0.6%) and decreased creatinine (1%). The common nonlaboratory grade 3 and grade 4 adverse events in the RT group treated with Alimta + cisplatin were fatigue (18.1%), nausea (14.6%), vomiting (13.7%), diarrhea (4.9%), dehydration (4.4%), stomatitis (4%), anorexia (3.5%) and rash (1.3%). In the FS group, the patients treated with Alimta + cisplatin had fatigue (17.3%), nausea (11.9%), vomiting (10.7%), dehydration (4.2%), diarrhea (3.6%), stomatitis (3%) and anorexia (2.4%). Supplementation with folic acid + vitamin B12 reduced many of the laboratory and non-laboratory toxicities in comparison to a never supplemented subgroup.

However, the demonstration of the survival benefit is based on only one randomized, control trial which had challenges with regard to pathology confirmation, eligibility based on measurable disease, response evaluation, the addition of folic acid plus vitamin B12 into the ongoing pivotal trial, and financial disclosure. In view that these deficiencies could be the result of bias and affect the survival benefit, replication of the survival benefit in another randomized, controlled trial appears desirable although not required for approval.

Based on this review of NDA 21-462, Alimta in combination with cisplatin is clinically approvable for the treatment of malignant pleural mesothelioma patients whose disease is either unresectable or who are not candidates for curative surgery.

2. Recommendation on Phase 4 Studies and/or Risk Management Steps

No clinical Phase 4 studies are recommended

II. Summary of Clinical Findings

1. Brief Overview of Clinical Program

Product name: ALIMTA (pemetrexed, MTA, LY231514) for injection
Class of Drug: antineoplastic (cytotoxic); antimetabolite (antifolate)
Route of Administration: Intravenous

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

Important Trials:

Protocol H3E-MC-JMCH(g): A Single-blind Randomized Phase 3 Trial of MTA[2] plus Cisplatin versus Cisplatin in Patients with Malignant Pleural Mesothelioma (Pivotal trial; reviewed by FDA)

Enrolled: 226 alimta plus cisplatin arm (168 folic acid + Vitamin B12 supplemented 168; 58 partially supplemented or never supplemented); 222 cisplatin alone arm (163 folic acid + Vitamin B12 supplemented, 59 partially supplemented or never supplemented).

Protocol H3E-MC-JMDR Phase 2: A Phase 2 Trial of LY231514 Administered Intravenously Every 21 Days in Patients with Malignant Pleural Mesothelioma (Supported trial; not reviewed by FDA)

Enrolled: 64 (43 folic acid + Vitamin B12 supplemented; 21 never supplemented)

2. Efficacy

In the pivotal trial, A Single-blind Randomized Phase 3 Trial of MTA[3] plus Cisplatin versus Cisplatin in Patients with Malignant Pleural Mesothelioma, survival was the primary endpoint. The following table illustrates the survival benefit achieved in this randomized, controlled trial.

GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Randomized and treated (n=448)	12.1 months	9.3 months	0.021
Fully folic acid/vitamin B12 supplemented (n=331))	13.3 months	10 months	0.051
Partial supplemented + never supplemented (n=117)	9.5 months	7.2 months	0.253
Intent-to-treat (n=456)	12 months	9.3 months	0.0205
Confirmed mesothelioma pathology Randomized and treated (n=303)	13 months	10.2 months	0.066

[2] alimta
[3] alimta

GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Confirmed mesothelioma pathology Fully folic acid/vitamin B12 supplemented (n=220)	14.4 months	10.3 months	0.058
Gender Female Randomized and treated (n=83)	15.7 months	7.5 months	0.012
Gender Female Fully folic acid/vitamin B12 supplemented (n=61)	18.9 months	7.4 months	0.01
Gender Male Randomized and treated (n=365)	11 months	9.4 months	0.176
Gender Male Fully folic acid/vitamin B12 supplemented (n=270)	12.8 months	10.4	0.388
Race White Randomized and treated (n=410)	12.2 months	9.3 monts	0.024
Race White Fully folic acid/vitamin B12 supplemented (n=303)	13.3 months	10.2 months	0.026
Race Non-white Randomized and treated (n=38)	9 months	8.4 months	0.715
Race Non-white Fully folic acid/vitamin B12 supplemented (n=28)	8.8 months	9.55 months	0.619
Age < 65 years Randomized and treated (n=279)	13.3 months	10.2 months	0.02

GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Age < 65 years Fully folic acid/vitamin B12 supplemented (n=204)	14.7 months	10.8 months	0.052
Age ≥ 65 years Randomized and treated (n=169)	10 months	7.5 months	0.376
Age ≥ 65 years Fully folic acid/vitamin B12 supplemented (n=127)	12.2 months	8.7 months	0.503

The data supports the following indication:

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

The combination of Alimta plus cisplatin is the first chemotheraupetic regimen to demonstrate a survival benefit in malignant pleural mesothelioma in comparison to a control regimen.

Response rate was a secondary endpoint for study JMCH. The following table illustrates the response rate demonstrated in patients with a confirmed pathological diagnosis of mesothelioma.

	ALIMTA + CISPLATIN, FDA CONFIRMED RESPONDERS			CISPLATIN ALONE, LILLY LISTED RESPONDERS		
	Proportion	Response rate	95% CI	Proportion	Response rate	95% CI
overall response rate	38/153	25%	18,32	25/149	17%	11,23
epithelial	35/130	27%	29,35	22/127	17%	11,24
Mixed	3/15	20%	-0.2,37	1/13	8%	-7,22
Sarcomatoid	0/8	0%		2/9	22%	-5, 49
folic acid/vitamin B12 supplementation	29/111	26%	18,34	21/108	19%	12,27
Partial supplementation	3/20	15%	-0.7,31	3/14	21%	-0.1, 43
never supplemented	6/22	27%	9,46	1/27	4%	-3,11

In contrast to the survival endpoint and although the response rate of the alimta + cisplatin arm was higher than the cisplatin alone arm, response rate was not a rigorous endpoint in study JMCH for a number of reasons.

At the End of Phase II meetings, the FDA indicated to Lilly that tumor response rate in mesothelioma could not be reliably assessed and that the FDA would not make any important decisions regarding efficacy based on tumor response rate or time to tumor progression.

3. Safety

The pivotal trial was a multicenter, randomized, single-blind Phase III trial in chemo-naïve patients with malignant pleural mesothelioma (MPM) treated with Alimta in combination with cisplatin compared to patients who received cisplatin alone. Alimta was administered at a dose of 500 mg/m^2 intravenously over approximately 10 minutes followed approximately 30 minutes later by cisplatin, 75 mg/ m^2 intravenously over approximately 2 hours on Day 1 of each 21- day cycle. In the cisplatin only arm, normal saline which did not contain Alimta was administered intravenously over approximately 10 minutes followed approximately 30 minutes later by cisplatin, 75 mg/ m^2 intravenously over approximately 2 hours on Day 1 of each 21- day cycle. Patients in both arms were pre- and post- hydrated according to local practice. Dexamethasone 4 mg, or equivalent corticosteroid was taken orally twice per day on the day before, the day of,

and the day after each dose of Alimta plus cisplatin. Folic acid supplementation, 350–1000 μg or equivalent was taken orally daily beginning approximately 1 to 3 weeks prior to the first dose of Alimta plus cisplatin and continued daily until the patient discontinued from study therapy. A vitamin B_{12} injection, 1000 μg was given intramuscularly approximately 1 to 3 weeks prior to the first dose of Alimta plus cisplatin and was repeated approximately every 9 weeks until the patient discontinued from study therapy.

The median age of patients at the time of randomization was 60 years. Although 456 patients were randomized, 8 patients did not receive the study drug; a total of 448 patients were treated and received at least one dose of study drug(s). The primary analysis of this study was performed on the population of all patients who received study drug in the treatment arm. A subgroup analysis was performed on patients who received folic acid and vitamin B_{12} supplementation during the entire course of study therapy. Randomized and treated patients completed a median of 6 cycles of the Alimta/cisplatin arm and 4 cycles of the cisplatin only arm. Supplemented patients completed a median of six cycles and nonsupplemented patients completed a median of 2 cycles of Alimta/cisplatin. The planned mean dose for Alimta and cisplatin were 166.7 and 25 $mg/m^2/wk$ respectively. The mean dose delivered was 153.4 $mg/m^2/wk$ of Alimta and 23.2 $mg/m^2/wk$ of cisplatin in the RT group and 154.6 $mg/m^2/wk$ and 23.4 $mg/m^2/wk$ in the FS group. When used alone, cisplatin was given at 24.1 $mg/m^2/wk$. The percent of planned dose intensity was 92/92.8% for Alimta/cisplatin in the RT group and 92.7/93.6% Alimta/cisplatin in the FS group. 96.4% of cisplatin alone could be given in both the RT and FS groups. In the RT group, 308 (28.9%) dose delays were reported in the Alimta/cisplatin arm and 171 (19.5%) in the cisplatin alone arm. Scheduling conflicts constituted the majority of dose delays. The most common clinical cause of dose delay on both arms was neutropenia. On both arms, cycle 4 was the cycle with the most delays. The common grade 3 or grade 4 laboratory toxicities in the RT group treated with Alimta/cisplatin were neutropenia (28.8%), leucopenia (18.1%), thrombocytopenia (5.8%) and anemia (6.2%); in the cisplatin only arm, neutropenia (2.3%), leucopenia (1.4%) and decreased creatinine (1%) were the common toxicites. In the FS group, the Alimta/cisplatin treated arm had neutropenia (24.4%), leucopenia (15.5%), anemia (6%), thrombocytopenia (5.4%) while the cisplatin only arm had neutropenia (3.1%), leucopenia (0.6%) and decreased creatinine (1%). The common nonlaboratory grade 3 and grade 4 adverse events in the RT group treated with Alimta/cisplatin were fatigue (18.1%), nausea (14.6%), vomiting (13.7%), diarrhea (4.9%), dehydration (4.4%), stomatitis (4%), anorexia (3.5%) and rash (1.3%). In the cisplatin alone arm the common adverse events were fatigue (15.3%), nausea (6.3%), and vomiting (3.6%). In the FS group, the patients treated with Alimta/cisplatin had fatigue (17.3%), nausea (11.9%), vomiting (10.7%), dehydration (4.2%), diarrhea (3.6%), stomatitis (3%) and anorexia (2.4%). Those in the cisplatin alone arm had fatigue (12.9%), nausea (5.5%) and vomiting (4.3%). A comparison between the two treatment arms in the FS group showed a statistically significant difference for neutrophils and leukocytes with more neutropenia and leucopenia in the Alimta/cisplatin group. Effect of supplementation reduced many of the laboratory and non-laboratory toxicities.

Use of vitamin supplementation by patients must be emphasized. Patients treated with Alimta must be instructed to take low-dose folic acid daily so that at least 5 doses are

taken during the 7-day period preceding the first dose of Alimta and continuing until 21 days after the last dose. Patients must also receive 1 injection of vitamin B_{12} during the week prior to receiving the first dose of Alimta and every 3 cycles thereafter during therapy. Subsequent vitamin B_{12} injections may be given the same day as Alimta. Alimta with dexamethasone or equivalent reduces the incidence and severity of cutaneous reactions.

As a class, folic acid antimetabolites have been demonstrated to produce manifestations of developmental toxicity such as growth retardation, embryo lethality, and malformations. Alimta was found to be embryo toxic at doses of 10 mg/ kg (30 mg/ m^2) and fetotoxic causing fetal malformations (cleft palate) at doses of 5 mg/ kg (15 mg/ m^2). There are no studies of Alimta in pregnant women. 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.

As with other anti-folate drugs, there is a potential for serious adverse reactions in nursing infants and nursing should be discontinued if the mother is treated with Alimta.

Alimta is eliminated primarily via the renal route. Patients with a creatinine clearance of < 45 ml/min, calculated with the mean body weight by the formula of Cockcroft and Gault, should not receive Alimta.

As with other antifolates, caution should be exercised when concomitant administration of Alimta with nonsteroidal anti-inflammatory drugs are used.

Patients with clinically significant pleural effusions have been excluded in studies performed with Alimta. Before starting treatment, pleural effusions should be drained.

The safety evaluation seems adequate for marketing for this indication. Areas of caution and limited safety experience have been noted above.

Extent of Exposure

Drug Administration

Of the 456 patients randomly assigned to a treatment arm, 448 (98.2%) received Alimta/ cisplatin or cisplatin monotherapy. These patients constitute the randomized and treated (RT) population for this study. Of these, 226 patients were randomized to and treated with Alimta/cisplatin and 222 patients were randomized to the cisplatin alone arm and received at least one dose of cisplatin. Among these 448 patients, 331 patients were fully supplemented and constituted the fully supplemented (FS) population for this study. Of the 331 patients, 168 were randomized and treated with Alimta/cisplatin and 163 were randomized and treated with cisplatin alone.

Among the RT patients, a median of six cycles (range: 1 – 12 cycles) were completed on the Alimta/ cisplatin arm compared with four cycles (range: 1 – 9 cycles) completed on the cisplatin alone arm. A total of 120 (53.1%) patients on the Alimta/ cisplatin arm and 89 (40.1%) patients on the cisplatin alone arm completed at least six cycles of therapy while 18 (8.0%) patients on the Alimta/ cisplatin arm compared with 19 (8.6%) patients on the cisplatin alone arm completed only one cycle. The duration of treatment was greater in the Alimta/cisplatin arm than in the cisplatin alone arm.

Among the FS patients, a median of six cycles of therapy were delivered on the Alimta/ cisplatin arm compared with four cycles delivered on the cisplatin alone arm. In addition, among FS patients, a total of 97 (57.7%) patients on the Alimta/ cisplatin arm versus 66 (40.5%) patients on the cisplatin alone arm completed at least six cycles of therapy. Thirteen (7.7%) patients on the Alimta/ cisplatin arm compared with 15 (9.2%) patients on the cisplatin alone arm completed only one cycle.

Within the Alimta/ cisplatin arm, FS patients received a median of six cycles compared with two cycles in the never-supplemented (NS) patients ($p=< 0.001$). For the cisplatin alone arm, there was also a difference favoring a larger number of cycles in the FS group ($p= 0.049$).

Among RT patients, 1066 cycles were administered to patients on the Alimta/cisplatin arm while 877 cycles were administered to patients on the cisplatin alone arm. On the Alimta/ cisplatin arm, 96.6% of the Alimta cycles and 96.5% of the cisplatin cycles were administered at full dose. On the cisplatin alone arm, 99.7% of cycles were given without any dose adjustment.

Alimta exposure was for a median of 18 weeks. The median doses of Alimta and cisplatin were higher in those fully supplemented. Patients in both arms received > 90% of the planned dose intensity. Patients receiving Alimta in the RT group received a relative dose intensity of 92% of the protocol specified Alimta dose intensity and patients treated with cisplatin in the same group received 92.3% of the projected dose intensity with Alimta compared to 96.5% cisplatin alone. Similarly, after supplementation, 92.7% Alimta, 93% cisplatin when given with Alimta and 96.4% cisplatin when given alone were the relative dose intensities.

4. Dosing

The results of the pivotal trial, JMCH, provided confidence in the efficacy and safety of alimta + cisplatin (plus folic acid and vitamin B12) in patients with malignant pleural mesothelioma. However, the underlying science of the addition of folic acid and B12 to an antifolate regimen did not provide confidence with known *in vitro* and *in vivo* antifolate pharmacology. This issue is discussed in

detail in section 5 (Important Issues with Pharmacologically Related Agents) of this review.

5. Special Populations

5.1 Gender, Race, and Age

Below are the survival analyses for gender, race, and age from the pivotal trial, study JMCH.

GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Gender Female Randomized and treated (n=83)	15.7 months	7.5 months	0.012
Gender Female Fully folic acid/vitamin B12 supplemented (n=61)	18.9 months	7.4 months	0.01
Gender Male Randomized and treated (n=365)	11 months	9.4 months	0.176
Gender Male Fully folic acid/vitamin B12 supplemented (n=270)	12.8 months	10.4	0.388
Race White Randomized and treated (n=410)	12.2 months	9.3 monts	0.024
Race White Fully folic acid/vitamin B12 supplemented (n=303)	13.3 months	10.2 months	0.026
Race Non-white Randomized and treated (n=38)	9 months	8.4 months	0.715
Race Non-white Fully folic acid/vitamin B12 supplemented (n=28)	8.8 months	9.55 months	0.619

GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Age < 65 years Randomized and treated (n=279)	13.3 months	10.2 months	0.02
Age < 65 years Fully folic acid/vitamin B12 supplemented (n=204)	14.7 months	10.8 months	0.052
Age ≥ 65 years Randomized and treated (n=169)	10 months	7.5 months	0.376
Age ≥ 65 years Fully folic acid/vitamin B12 supplemented (n=127)	12.2 months	8.7 months	0.503

The under-powered female subgroup demonstrated in randomized and treated and the fully folic acid/vitamin B12 supplemented groups a statistically significant survival advantage in favor of the alimta/cisplatin; a similar analysis in the much larger male subgroup demonstrated only trends in favor of the alimta/cisplatin arm[4]. The white subgroup demonstrated, in the randomized and treated and the fully folic acid/vitamin B12 supplemented groups, a statistically significant survival advantage in favor of the alimta/cisplatin; the under-powered non-white group demonstrated a trend in favor of alimta/cisplatin in the randomized and treated group and trend in favor of cisplatin in the fully folic acid/vitamin B12 supplemented group. The age < 65 years subgroup demonstrated, in the randomized and treated and the fully folic acid/vitamin B12 supplemented groups, a survival advantage in favor of the alimta/cisplatin that was statistically significant and marginally significant, respectively. The age ≥ 65 years subgroup demonstrated trends in favor of the alimta/cisplatin arm.

5.2 Pregnancy and Nursing

As a class, folic acid antimetabolites have been demonstrated to produce manifestations of developmental toxicity such as growth retardation, embryo lethality, and malformations. Alimta was found to be embryo toxic at doses of 10 mg/ kg (30 mg/ m^2) and fetotoxic causing fetal malformations (cleft palate) at doses of 5 mg/ kg (15 mg/ m^2). There are no studies of Alimta in pregnant women. 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.

[4] Lilly did a multifactorial survival analysis considering prognostic factors and there was no gender effect; ISE document submitted 3/24/2003.

Clinical Review

I. Introduction and Background

1. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Product name: ALIMTA (pemetrexed, MTA, LY231514) for injection

Drug Class: antineoplastic (cytotoxic); antimetabolite (antifolate)

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

Regimen:

- ALIMTA, 500 mg/m^2 administered as an intravenous infusion over 10 minutes on day 1 of each 21-day cycle.
- Cisplatin, 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.
- Premedication Regimen

  dexamethasone 4 mg was given by mouth twice daily the day before, the day of, and the day after ALIMTA administration.

  Folic acid (at least 5 daily doses must be taken during the 7-day period preceding the first dose of ALIMTA) 350 to 1000 µg orally per day; folic acid dosing should continue during the full course of therapy and for 21 days after the last dose of ALIMTA.

  Vitamin B_{12} 1000 µg by intramuscular injection during the week preceding the first dose of ALIMTA; vitamin B12 is repeated every 3 cycles thereafter.

Age group: greater than 18 years of age

2. State of Armamentarium for Indication

There are no other approved chemotherapeutic agents for malignant pleural mesothelioma.

3. Important Milestones in Product Development--From IND to NDA

	MEETING, SUBMISSION, OR ACTION	INDICATION, PROTOCOL, ISSUES	AGREEMENTS OR FDA RECOMMENDATIONS
July 8, 1992	Original IND submission	Phase 1 trial of LY231514 administered as a bolus infusion every 7 days proposed starting dose: 40 mg/m2	
August 7, 1992	Clinical hold		Animal data does not support proposed starting dose
September 11, 1992	Removal of clinical hold		New proposed starting dose: 10 mg/m2 (DLT @ 40 mg/m2)
September 25, 1998	1st End of Phase 2 meeting	Indication: treatment of pleural mesothelioma[5] 600 mg/m2 vs. 500 mg/m2 dose q 3 wks Endpoints for mesothelioma: reesponse rate, clinical benefit Accelerated approval based on response rate	 FDA advice: 500 mg/m2 FDA advice: survival as primary endpoint; blinded study; addition of vitamins to MTA without data that efficacy is not reduced is risky Survival (superior) as the endpoint for full approval or clinical benefit (e.g., reduction in pain, shortness of breath, tumor-related symptoms) in a blinded trial

[5] There was also a discussion of NSCLC: Treatment of advanced NSLC whose disease has recurred or progressed following platin- or taxane based therapy

	MEETING, SUBMISSION, OR ACTION	INDICATION, PROTOCOL, ISSUES	AGREEMENTS OR FDA RECOMMENDATIONS
		Unidimensional measurements will provide sufficient information for response	FDA uncertain Two studies for mesothelioma lead indication; confirmatory evidence may come from a closely related disease, i.e., NSCLC
December 3, 1998 Serial #149	Telecon in follow-up to 9/28/98 EOP2 meeting	Double-blinding problematic: Placebo approval by foreign regulatory authorities was a problem	Division not familiar with placebo restrictions in other countries Sponsor to go back to foreign regulatory authorities and submit a proposal to the Division
December 18, 1998	Telecon in follow-up to 9/28/98 EOP2 meeting and 12/3/98 telecon	European investigators will not do a double-blinded trial	Improved clinical benefit would be considered more robust in a double-blind trial Sponsor to submit a proposal describing how a single-blinded study of clinical benefit would be appropriated for study JMCH
February 12, 1999 Serial #150	Single blinded study with clinical benefit as basis for full approval Mesothelioma protocol review	A single-blind muti-center randomized Phase III study in patients with malignant pleural mesothelioma Interim analysis comparing clinical	FDA: • Double-blinded trial • Separate assessment of each component of clinical benefit endpoint

	MEETING, SUBMISSION, OR ACTION	INDICATION, PROTOCOL, ISSUES	AGREEMENTS OR FDA RECOMMENDATIONS
		benefit response on 75 qualified patients per arms Efficacy analysies will be perfomed on intent-to-treat population Survival will be primary endpoint	2nd pivotal trial in mesothelioma: cisplatin + MTA vs. cisplatin + gemcitabine; superior survival
April 23, 1999	1st patient entered on JMCH		
May 12, 1999	1st patient randomized on JMCH		
June 25, 1999	2nd End of Phase 2 meeting	Indication: MTA in patients with mesothelioma Unidimensional tumor measurements Response rate, TTP, clinical benefit as endpoints for accelerated approval Submission of NDA based on interim analysis of response rate, TTP, and clinical benefit	See EOP2 meeting 9/23/98 FDA: Survival is the primary endpoint; full survival data to be submitted with NDA If clinical benefit is to suffice for approval: double-blinding strongly advised Commitment to complete 280-patient trial even if results are positive at interim analysis because clinical benefit has not been shown to correlate with survival Confirmatory evidence from a closely related disease, i.e., NSCLC FDA urged Lilly to design

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			a 2nd RCT in pleural mesothelioma Positive evidence of clinical efficacy for TTP, CB, or RR at interim analysis + Phase 2 data FDA: Phase 2 data from mesothelioma would be supportive if responses can be convincingly demonstrated Rolling submission under Fast Track: review clock starts when submission complete
November 8 and December 3, 1999 FDA response faxed 12/21/99	Protocol amendment Serial #191 and #195	Proposed adding vitamins to ongoing mesothelioma trial	Disagreement with addition of vitamins: • No statistical plan • Commitment to completing 280-patient trial FDA proposed MTA ± vitamins trial
December 2, 1999	Implementation of vitamin supplementation		
December 22, 1999	Serial #200 and #201	Proposed adding vitamins to ongoing mesothelioma trial	Non-support for adding vitamins to the ongoing mesothelioma registration trial
March 1, 2000	3rd End of Phase 2 meeting	MTA in patients with mesothelioma Proposed addition of vitamins to ongoing	FDA options: 1. Temporarily closing