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ALIMTA[®]

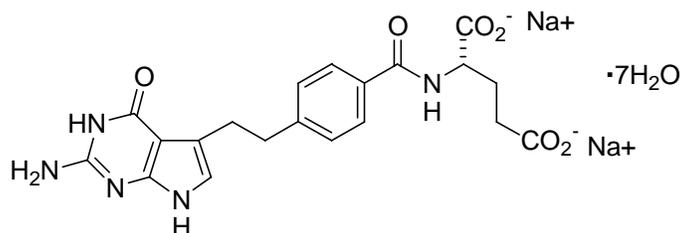
pemetrexed

for injection

5

DESCRIPTION

6 ALIMTA[®], pemetrexed for injection, is an antifolate antineoplastic agent that exerts its action
7 by disrupting folate-dependent metabolic processes essential for cell replication. Pemetrexed
8 disodium heptahydrate has the chemical name L-Glutamic acid, *N*-[4-[2-(2-amino-4,7-dihydro-4-
9 oxo-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate. It is a white
10 to almost-white solid with a molecular formula of C₂₀H₁₉N₅Na₂O₆•7H₂O and a molecular weight
11 of 597.49. The structural formula is as follows:



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

17

CLINICAL PHARMACOLOGY

18

Pharmacodynamics

19 Pemetrexed is an antifolate containing the pyrrolopyrimidine-based nucleus that exerts its
20 antineoplastic activity by disrupting folate-dependent metabolic processes essential for cell
21 replication. In vitro studies have shown that pemetrexed inhibits thymidylate synthase (TS),
22 dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT),
23 all folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine
24 nucleotides. Pemetrexed is transported into cells by both the reduced folate carrier and
25 membrane folate binding protein transport systems. Once in the cell, pemetrexed is converted to
26 polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are
27 retained in cells and are inhibitors of TS and GARFT. Polyglutamation is a time- and
28 concentration-dependent process that occurs in tumor cells and, to a lesser extent, in normal
29 tissues. Polyglutamated metabolites have an increased intracellular half-life resulting in
30 prolonged drug action in malignant cells.

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

34 Absolute neutrophil counts (ANC) following single-agent administration of pemetrexed to
35 patients not receiving folic acid and vitamin B₁₂ supplementation were characterized using
36 population pharmacodynamic analyses. Severity of hematologic toxicity, as measured by the
37 depth of the ANC nadir, correlates with the systemic exposure of pemetrexed. It was also
38 observed that lower ANC nadirs occurred in patients with elevated baseline cystathionine or
39 homocysteine concentrations. The levels of these substances can be reduced by folic acid and
40 vitamin B₁₂ supplementation. There is no cumulative effect of pemetrexed exposure on ANC
41 nadir over multiple treatment cycles.

42 Time to ANC nadir with pemetrexed systemic exposure (AUC), varied between 8 to 9.6 days
43 over a range of exposures from 38.3 to 316.8 $\mu\text{g}\cdot\text{hr}/\text{mL}$. Return to baseline ANC occurred 4.2 to
44 7.5 days after the nadir over the same range of exposures.

45 **Pharmacokinetics**

46 The pharmacokinetics of pemetrexed administered as a single agent in doses ranging from
47 0.2 to 838 mg/m^2 infused over a 10-minute period have been evaluated in 426 cancer patients
48 with a variety of solid tumors. Pemetrexed is not metabolized to an appreciable extent and is
49 primarily eliminated in the urine, with 70% to 90% of the dose recovered unchanged within the
50 first 24 hours following administration. The total systemic clearance of pemetrexed is
51 91.8 mL/min and the elimination half-life of pemetrexed is 3.5 hours in patients with normal
52 renal function (creatinine clearance of 90 mL/min). The clearance decreases, and
53 exposure (AUC) increases, as renal function decreases. Pemetrexed total systemic
54 exposure (AUC) and maximum plasma concentration (C_{max}) increase proportionally with dose.
55 The pharmacokinetics of pemetrexed do not change over multiple treatment cycles. Pemetrexed
56 has a steady-state volume of distribution of 16.1 liters. In vitro studies indicate that pemetrexed
57 is approximately 81% bound to plasma proteins. Binding is not affected by degree of renal
58 impairment.

59 **Drug Interactions**

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

62 *Vitamins* — Coadministration of oral folic acid or intramuscular vitamin B₁₂ does not affect the
63 pharmacokinetics of pemetrexed.

64 *Drugs Metabolized by Cytochrome P450 Enzymes* — Results from in vitro studies with human
65 liver microsomes predict that pemetrexed would not cause clinically significant inhibition of
66 metabolic clearance of drugs metabolized by CYP3A, CYP2D6, CYP2C9, and CYP1A2. No
67 studies were conducted to determine the cytochrome P450 isozyme induction potential of
68 pemetrexed, because ALIMTA used as recommended (once every 21 days) would not be
69 expected to cause any significant enzyme induction.

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

73 *Ibuprofen* — Daily ibuprofen doses of 400 mg qid reduce pemetrexed's clearance by about
74 20% (and increase AUC by 20%) in patients with normal renal function. The effect of greater
75 doses of ibuprofen on pemetrexed pharmacokinetics is unknown (*see Drug Interactions under*
76 **PRECAUTIONS**).

77 **Special Populations**

78 The pharmacokinetics of pemetrexed in special populations were examined in about
79 400 patients in controlled and single arm studies.

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

82 *Pediatric* — Pediatric patients were not included in clinical trials.

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

85 *Race* — The pharmacokinetics of pemetrexed were similar in Caucasians and patients of
86 African descent. Insufficient data are available to compare pharmacokinetics for other ethnic
87 groups.

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

91 *Renal Insufficiency* — Pharmacokinetic analyses of pemetrexed included 127 patients with
 92 reduced renal function. Plasma clearance of pemetrexed decreases as renal function decreases,
 93 with a resultant increase in systemic exposure. Patients with creatinine clearances of 45, 50, and
 94 80 mL/min had 65%, 54%, and 13% increases, respectively in pemetrexed total systemic
 95 exposure (AUC) compared to patients with creatinine clearance of 100 mL/min (*see*
 96 **WARNINGS and DOSAGE AND ADMINISTRATION**).

97 **CLINICAL STUDIES**

98 *Malignant Pleural Mesothelioma* — The safety and efficacy of ALIMTA have been evaluated
 99 in chemo-naïve patients with malignant pleural mesothelioma (MPM) in combination with
 100 cisplatin.

101 **Randomized Trial:** A multi-center, randomized, single-blind study in 448 chemo-naïve patients
 102 with MPM compared survival in patients treated with ALIMTA in combination with cisplatin to
 103 survival in patients receiving cisplatin alone. ALIMTA was administered intravenously over
 104 10 minutes at a dose of 500 mg/m² and cisplatin was administered intravenously over 2 hours at
 105 a dose of 75 mg/m² beginning approximately 30 minutes after the end of administration of
 106 ALIMTA. Both drugs were given on Day 1 of each 21-day cycle. After 117 patients were
 107 treated, white cell and GI toxicity led to a change in protocol whereby all patients were given
 108 folic acid and vitamin B₁₂ supplementation.

109 The primary analysis of this study was performed on the population of all patients randomly
 110 assigned to treatment who received study drug (randomized and treated). An analysis was also
 111 performed on patients who received folic acid and vitamin B₁₂ supplementation during the entire
 112 course of study therapy (fully supplemented), as supplementation is recommended (*see*
 113 **DOSAGE AND ADMINISTRATION**). Results in all patients and those fully supplemented
 114 were similar. Patient demographics are shown in Table 1.
 115

Table 1: Summary of Patient Characteristics in MPM Study

Patient characteristic	Randomized and Treated Patients		Fully Supplemented Patients	
	ALIMTA/cis (N=226)	Cisplatin (N=222)	ALIMTA/cis (N=168)	Cisplatin (N=163)
Age (yrs)				
Median (range)	61 (29-85)	60 (19-84)	60 (29-85)	60 (19-82)
Gender (%)				
Male	184 (81.4)	181 (81.5)	136 (81.0)	134 (82.2)
Female	42 (18.6)	41 (18.5)	32 (19.0)	29 (17.8)
Origin (%)				
Caucasian	204 (90.3)	206 (92.8)	150 (89.3)	153 (93.9)
Hispanic	11 (4.9)	12 (5.4)	10 (6.0)	7 (4.3)
Asian	10 (4.4)	4 (1.9)	7 (4.2)	3 (1.8)
African descent	1 (0.4)	0	1 (0.6)	0
Stage at Entry (%)				
I	16 (7.1)	14 (6.3)	15 (8.9)	12 (7.4)
II	35 (15.6)	33 (15.0)	27 (16.2)	27 (16.8)
III	73 (32.4)	68 (30.6)	51 (30.5)	49 (30.4)

IV	101 (44.9)	105 (47.2)	74 (44.3)	73 (45.3)
Unspecified	1 (0.4)	2 (0.9)	1 (0.6)	2 (1.2)
Diagnosis/Histology^a (%)				
Epithelial	154 (68.1)	152 (68.5)	117 (69.6)	113 (69.3)
Mixed	37 (16.4)	36 (16.2)	25 (14.9)	25 (15.3)
Sarcomatoid	18 (8.0)	25 (11.3)	14 (8.3)	17 (10.4)
Other	17 (7.5)	9 (4.1)	12 (7.1)	8 (4.9)
Baseline KPS^b (%)				
70-80	109 (48.2)	97 (43.7)	83 (49.4)	69 (42.3)
90-100	117 (51.8)	125 (56.3)	85 (50.6)	94 (57.7)

^a Only 67% of the patients had the histologic diagnosis of malignant mesothelioma confirmed by independent review.

^b Karnofsky Performance Scale.

Table 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 clear whether this difference is real or is a chance finding.

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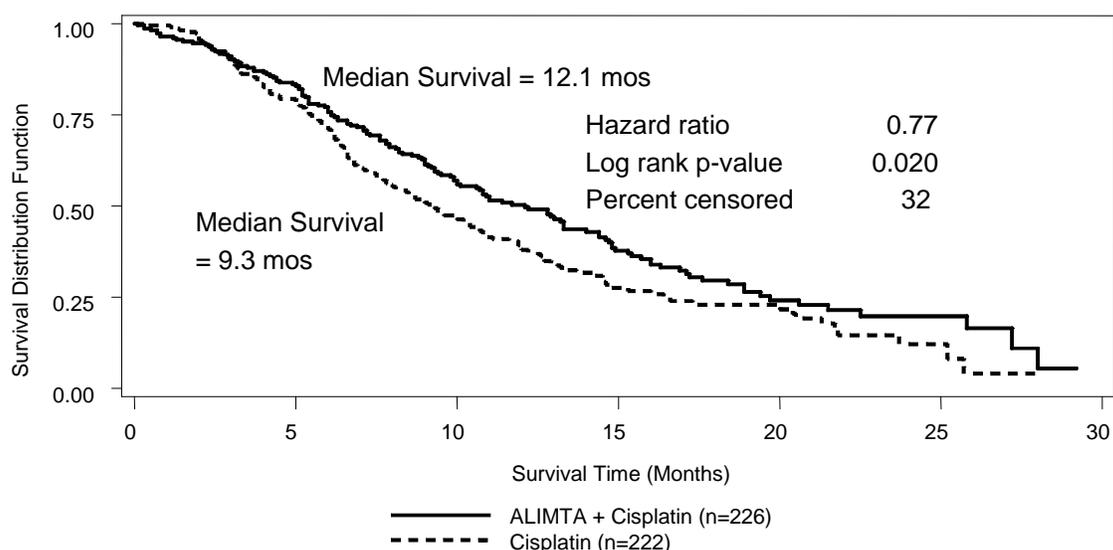


Figure 1: Kaplan-Meier Estimates of Survival Time for ALIMTA plus Cisplatin and Cisplatin Alone in all Randomized and Treated Patients.

134

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

140 Patients who received full supplementation with folic acid and vitamin B₁₂ during study
 141 therapy received a median of 6 and 4 cycles in the ALIMTA/cisplatin (N=168) and
 142 cisplatin (N=163) arms, respectively. Patients who never received folic acid and vitamin B₁₂
 143 during study therapy received a median of 2 cycles in both treatment arms (N=32 and N=38 for
 144 the ALIMTA/cisplatin and cisplatin arm, respectively). Patients receiving ALIMTA in the fully
 145 supplemented group received a relative dose intensity of 93% of the protocol specified ALIMTA
 146 dose intensity; patients treated with cisplatin in the same group received 94% of the projected
 147 dose intensity. Patients treated with cisplatin alone had a dose intensity of 96%.

148 *Non-Small Cell Lung Cancer (NSCLC)* — The safety and efficacy of ALIMTA as a
 149 single-agent have been evaluated in patients with locally advanced or metastatic (Stage III or IV)
 150 non-small cell lung cancer after prior chemotherapy.

151 **Randomized Trial:** A multi-center, randomized, open label Phase 3 study was conducted to
 152 compare the overall survival following treatment with ALIMTA versus docetaxel. ALIMTA was
 153 administered intravenously over 10 minutes at a dose of 500 mg/m² and docetaxel was
 154 administered at 75 mg/m² as a 1-hour intravenous infusion. Both drugs were given on Day 1 of
 155 each 21-day cycle. All patients treated with ALIMTA received vitamin supplementation with
 156 folic acid and vitamin B₁₂. The study was intended to show either an overall survival superiority
 157 or non-inferiority of ALIMTA to docetaxel. Patient demographics of the intent to treat (ITT)
 158 population are shown in Table 3.

159

Table 3: Summary of Patient Characteristics in NSCLC Study

Patient characteristic	ALIMTA (N=283)	Docetaxel (N=288)
Age (yrs)		
Median (range)	59 (22-81)	57 (28-87)
Gender (%)		
Male/Female	68.6/31.4	75.3/24.7
Stage at Entry (%)		
III/IV	25.1/74.9	25.3/74.7
Diagnosis/Histology (%)		
Adenocarcinoma	154 (54.4)	142 (49.3)
Squamous	78 (27.6)	93 (32.3)
Bronchoalveolar	4 (1.4)	1 (0.3)
Other	51 (18.1)	53 (18.5)
Performance Status (%)		
0-1	234 (88.6)	240 (87.6)
2	30 (11.4)	34 (12.4)

160

161 The primary endpoint in this study was overall survival. The median survival time was
162 8.3 months in the ALIMTA treatment arm and 7.9 months in the docetaxel arm, with a hazard
163 ratio of 0.99 (*see* Table 4). The study did not show an overall survival superiority of ALIMTA.
164 Non-inferiority of ALIMTA to docetaxel could not be demonstrated, because a reliable and
165 consistent survival effect of docetaxel required for a non-inferiority analysis could not be
166 estimated from historical trials. In addition, significant treatment crossover at the time of disease
167 progression may have confounded the survival interpretation. The demonstrated surrogate
168 endpoint, response rate allowed the conclusion that an effect of ALIMTA on survival is
169 reasonably likely.

170 Exploratory demographic analyses on survival showed no significant differences between
171 ALIMTA and docetaxel in patients over or under 65 years of age. There were too few non-white
172 patients to assess possible ethnic differences. Regarding gender, females lived longer than males
173 in both treatment groups. There was no difference in survival between ALIMTA and docetaxel
174 with respect to gender after adjusting for prognostic factors.

175 Secondary endpoints evaluated in the trial include objective response rate, progression free
176 survival (PFS) and time to progressive disease (TTPD). There was no statistically significant
177 difference between ALIMTA and docetaxel with respect to objective response rate, progression
178 free survival (PFS) and time to progressive disease (TTPD).

179

Table 4: Efficacy of ALIMTA vs. Docetaxel in Non-Small Cell Lung Cancer – ITT Population

	ALIMTA (N=283)	Docetaxel (N=288)
Median overall survival (95% CI)	8.3 mos (7.0-9.4)	7.9 mos (6.3-9.2)
Hazard ratio (HR) (95% CI)	0.99 ^a (0.82-1.20)	
Log rank p-value	0.93	
1-year survival (95% CI)	29.7% (23.7-35.6)	29.7% (23.9-35.5)
Median progression free survival	2.9 mos	2.9 mos
Hazard ratio (HR) (95% CI)	0.97 ^a (0.82-1.16)	

180

181

Time to Progressive Disease	3.4 mos	3.5 mos
Hazard ratio (HR) (95% CI)	0.97 ^a (0.80-1.17)	
Overall response rate ^{a,b} (95% CI)	9.1% (5.9-13.2)	8.8% (5.7-12.8)

^a Not statistically significant.

^b Number of qualified patients on the ALIMTA arm (N=264) and docetaxel arm (N=274).

INDICATIONS AND USAGE

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

Non-Small Cell Lung Cancer: ALIMTA as a single-agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

The effectiveness of ALIMTA in second-line NSCLC was based on the surrogate endpoint, response rate. There are no controlled trials demonstrating a clinical benefit, such as a favorable survival effect or improvement of disease-related symptoms.

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 ≥ 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 B₁₂ died of drug-related toxicity following administration of ALIMTA alone.

Bone Marrow Suppression

ALIMTA can suppress bone marrow function, as manifested by neutropenia, thrombocytopenia, and anemia (or pancytopenia) (*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 B₁₂ Supplementation

Patients treated with ALIMTA must be instructed to take folic acid and vitamin B₁₂ 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 B₁₂ 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.p. doses of 0.2 mg/kg (0.6 mg/m²) or 5 mg/kg (15 mg/m²) 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

225 on a mg/m² basis), and cleft palate at 5 mg/kg (about 1/33 the recommended i.v. human dose on
226 a mg/m² basis). Embryotoxicity was characterized by increased embryo-fetal deaths and reduced
227 litter sizes. There are no studies of ALIMTA in pregnant women. Patients should be advised to
228 avoid becoming pregnant. If ALIMTA is used during pregnancy, or if the patient becomes
229 pregnant while taking ALIMTA, the patient should be apprised of the potential hazard to the
230 fetus.

231

PRECAUTIONS

232 General

233 ALIMTA should be administered under the supervision of a qualified physician experienced in
234 the use of antineoplastic agents. Appropriate management of complications is possible only
235 when adequate diagnostic and treatment facilities are readily available. Treatment-related
236 adverse events of ALIMTA seen in clinical trials have been reversible. Skin rash has been
237 reported more frequently in patients not pretreated with a corticosteroid in clinical trials.
238 Pretreatment with dexamethasone (or equivalent) reduces the incidence and severity of
239 cutaneous reaction (*see* **DOSAGE AND ADMINISTRATION**).

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

243 Laboratory Tests

244 Complete blood cell counts, including platelet counts and periodic chemistry tests, should be
245 performed on all patients receiving ALIMTA. Patients should be monitored for nadir and
246 recovery, which were tested in the clinical study before each dose and on days 8 and 15 of each
247 cycle. Patients should not begin a new cycle of treatment unless the ANC is ≥ 1500 cells/mm³,
248 the platelet count is $\geq 100,000$ cells/mm³, and creatinine clearance is ≥ 45 mL/min.

249 Drug Interactions

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

254 Although ibuprofen (400 mg qid) can be administered with ALIMTA in patients with normal
255 renal function (creatinine clearance ≥ 80 mL/min), caution should be used when administering
256 ibuprofen concurrently with ALIMTA to patients with mild to moderate renal insufficiency
257 (creatinine clearance from 45 to 79 mL/min). Patients with mild to moderate renal insufficiency
258 should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the
259 day of, and 2 days following administration of ALIMTA.

260 In the absence of data regarding potential interaction between ALIMTA and NSAIDs with
261 longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least 5 days
262 before, the day of, and 2 days following ALIMTA administration. If concomitant administration
263 of an NSAID is necessary, patients should be monitored closely for toxicity, especially
264 myelosuppression, renal, and gastrointestinal toxicity.

265 Drug/Laboratory Test Interactions

266 None known.

267 Carcinogenesis, Mutagenesis, Impairment of Fertility

268 No carcinogenicity studies have been conducted with pemetrexed. Pemetrexed was clastogenic
269 in the in vivo micronucleus assay in mouse bone marrow but was not mutagenic in multiple
270 in vitro tests (Ames assay, CHO cell assay). Pemetrexed administered at i.v. doses of

271 0.1 mg/kg/day or greater to male mice (about 1/1666 the recommended human dose on a mg/m²
272 basis) resulted in reduced fertility, hypospermia, and testicular atrophy.

273 **Pregnancy**

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

275 **Nursing Mothers**

276 It is not known whether ALIMTA or its metabolites are excreted in human milk. Because
277 many drugs are excreted in human milk, and because of the potential for serious adverse
278 reactions in nursing infants from ALIMTA, it is recommended that nursing be discontinued if the
279 mother is treated with ALIMTA.

280 **Pediatric Use**

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

282 **Geriatric Use**

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

286 **Gender**

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

290 **Patients with Hepatic Impairment**

291 Patients with bilirubin >1.5 times the upper limit of normal were excluded from clinical trials
292 of ALIMTA. Patients with transaminase >3.0 times the upper limit of normal were routinely
293 excluded from clinical trials if they had no evidence of hepatic metastases. Patients with
294 transaminase from 3 to 5 times the upper limit of normal were included in the clinical trial of
295 ALIMTA if they had hepatic metastases.

296 Dose adjustments based on hepatic impairment experienced during treatment with ALIMTA
297 are provided in Table 9 (*see* **Special Populations under CLINICAL PHARMACOLOGY and**
298 **DOSAGE AND ADMINISTRATION**).

299 **Patients with Renal Impairment**

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

305 **ADVERSE REACTIONS**

306 *Malignant Pleural Mesothelioma* — In Table 5 adverse events occurring in at least 5% of
307 patients are shown along with important effects (renal failure, infection) occurring at lower rates.
308 Adverse events equally or more common in the cisplatin group are not included. The adverse
309 effects more common in the ALIMTA group were primarily hematologic effects, fever and
310 infection, stomatitis/pharyngitis, and rash/desquamation.

311

**Table 5: Adverse Events* in Fully Supplemented Patients Receiving ALIMTA plus
Cisplatin in MPM
CTC Grades (% incidence)**

	All Reported Adverse Events Regardless of Causality
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	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.

312
313

314 Table 6 compares the incidence (percentage of patients) of CTC Grade 3/4 toxicities in patients
315 who received vitamin supplementation with daily folic acid and vitamin B₁₂ from the time of
316 enrollment in the study (fully supplemented) with the incidence in patients who never received
317 vitamin supplementation (never supplemented) during the study in the ALIMTA plus
318 cisplatin arm.

319

Table 6: Selected Grade 3/4 Adverse Events Comparing Fully Supplemented versus Never Supplemented Patients in the ALIMTA plus Cisplatin arm in MPM (% incidence)

Adverse Event Regardless of Causality ^a (%)	Fully Supplemented Patients (N=168)	Never Supplemented Patients (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).

320
321

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

325 For fully supplemented patients treated with ALIMTA plus cisplatin, the incidence of CTC
326 Grade 3/4 fatigue, leukopenia, neutropenia, and thrombocytopenia were greater in patients
327 65 years or older as compared to patients younger than 65. No relevant effect for ALIMTA
328 safety due to gender or race was identified, except an increased incidence of rash in men (24%)
329 compared to women (16%).

330 *Non-Small Cell Lung Cancer (NSCLC)* — Table 7 provides the clinically relevant undesirable
331 effects that have been reported in 265 patients randomly assigned to receive single-agent
332 ALIMTA with folic acid and vitamin B₁₂ supplementation and 276 patients randomly assigned to
333 receive single-agent docetaxel. All patients were diagnosed with locally advanced or metastatic
334 NSCLC and had received prior chemotherapy.

**Table 7: Adverse Events* in Patients Receiving ALIMTA vs. Docetaxel in NSCLC
CTC Grades (% incidence)**

	All Reported Adverse Events Regardless of Causality					
	ALIMTA (N=265)			Docetaxel (N=276)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory						
Hematologic						
Anemia	33	6	2	33	6	<1
Leukopenia	13	4	<1	34	17	11
Neutropenia	11	3	2	45	8	32
Thrombocytopenia	9	2	0	1	1	0
Hepatic/Renal						
ALT elevation	10	2	1	2	<1	0
AST elevation	8	<1	1	1	<1	0
Decreased creatinine clearance	5	1	0	1	0	0
Creatinine elevation	3	0	0	1	0	0
Renal failure	<1	0	0	<1	0	0
Clinical						
Constitutional Symptoms						
Fatigue	87	14	2	81	16	1
Fever	26	1	<1	19	<1	0
Edema	19	<1	0	24	<1	0
Myalgia	13	2	0	20	3	0
Alopecia	11	NA	NA	42	NA	NA
Arthralgia	8	<1	0	13	3	0
Other constitutional symptoms	8	1	1	6	1	<1
Cardiovascular General						
Thrombosis/embolism	4	2	1	3	2	1
Cardiac ischemia	3	2	1	2	<1	0
Gastrointestinal						
Anorexia	62	4	1	58	7	<1
Nausea	39	4	0	25	3	0
Constipation	30	0	0	23	1	0
Vomiting	25	2	0	19	1	0
Diarrhea without colostomy	21	<1	0	34	4	0
Stomatitis/pharyngitis	20	1	0	23	1	0
Dysphagia/esophagitis/ odynophagia	5	1	<1	7	1	0
Dehydration	3	1	0	4	1	0

Pulmonary						
Dyspnea	72	14	4	74	17	9
Pain						
Chest pain	38	6	<1	32	7	<1
Neurology						
Neuropathy/sensory	29	2	0	32	1	0
Mood alteration/depression	11	0	<1	10	1	0
Infection/Febrile Neutropenia						
Infection without neutropenia	23	5	<1	17	3	1
Infection/febrile neutropenia-other	6	2	0	2	<1	0
Febrile neutropenia	2	1	1	14	10	3
Infection with Grade 3 or Grade 4 neutropenia	<1	0	0	6	4	1
Immune						
Allergic reaction/hypersensitivity	8	0	0	8	1	<1
Dermatology/Skin						
Rash/desquamation	17	0	0	9	0	0

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

336
337

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

345 The incidence of CTC Grade 3/4 hypertension was the only finding demonstrating an age
346 difference in patients treated with ALIMTA and was greater in patients 65 years or older as
347 compared to younger patients. There are insufficient numbers of non-white patients to assess
348 ethnic differences. The incidence of CTC Grade 3/4 dyspnea was higher in males for both
349 treatment arms.

350 **Post-marketing experience:** The following adverse events have been identified during
351 post-approval use of ALIMTA. These events have occurred with ALIMTA when used as a
352 single-agent and in combination therapies. Decisions to include these events are based on the
353 seriousness of the event, frequency of reporting, or potential causal connection to ALIMTA.

354 *Gastrointestinal* — Rare cases of colitis have been reported in patients treated with ALIMTA.

355 OVERDOSAGE

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

362 In clinical trials, leucovorin was permitted for CTC Grade 4 leukopenia lasting ≥ 3 days,
363 CTC Grade 4 neutropenia lasting ≥ 3 days, and immediately for CTC Grade 4 thrombocytopenia,
364 bleeding associated with Grade 3 thrombocytopenia, or Grade 3 or 4 mucositis. The following
365 intravenous doses and schedules of leucovorin were recommended for intravenous use:
366 100 mg/m^2 , intravenously once, followed by leucovorin, 50 mg/m^2 , intravenously every 6 hours
367 for 8 days.

368 The ability of ALIMTA to be dialyzed is unknown.

369 **DOSAGE AND ADMINISTRATION** 370 **ALIMTA is for Intravenous Infusion Only**

371 **Combination Use With Cisplatin**

372 *Malignant Pleural Mesothelioma* — The recommended dose of ALIMTA is 500 mg/m^2
373 administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle. The
374 recommended dose of cisplatin is 75 mg/m^2 infused over 2 hours beginning approximately
375 30 minutes after the end of ALIMTA administration. Patients should receive hydration consistent
376 with local practice prior to and/or after receiving cisplatin. See cisplatin package insert for more
377 information.

378 **Single-Agent Use**

379 *Non-Small Cell Lung Cancer* — The recommended dose of ALIMTA is 500 mg/m^2
380 administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle.

381 **Premedication Regimen**

382 *Corticosteroid* — Skin rash has been reported more frequently in patients not pretreated with a
383 corticosteroid. Pretreatment with dexamethasone (or equivalent) reduces the incidence and
384 severity of cutaneous reaction. In clinical trials, dexamethasone 4 mg was given by mouth
385 twice daily the day before, the day of, and the day after ALIMTA administration.

386 *Vitamin Supplementation* — To reduce toxicity, patients treated with ALIMTA must be
387 instructed to take a low-dose oral folic acid preparation or multivitamin with folic acid on a daily
388 basis. At least 5 daily doses of folic acid must be taken during the 7-day period preceding the
389 first dose of ALIMTA; and dosing should continue during the full course of therapy and for
390 21 days after the last dose of ALIMTA. Patients must also receive one (1) intramuscular
391 injection of vitamin B₁₂ during the week preceding the first dose of ALIMTA and every 3 cycles
392 thereafter. Subsequent vitamin B₁₂ injections may be given the same day as ALIMTA. In clinical
393 trials, the dose of folic acid studied ranged from 350 to 1000 μg , and the dose of vitamin B₁₂ was
394 1000 μg . The most commonly used dose of oral folic acid in clinical trials was 400 μg (*see*
395 **WARNINGS**).

396 **Laboratory Monitoring and Dose Reduction Recommendations**

397 *Monitoring* — Complete blood cell counts, including platelet counts, should be performed on
398 all patients receiving ALIMTA. Patients should be monitored for nadir and recovery, which were
399 tested in the clinical study before each dose and on days 8 and 15 of each cycle. Patients should
400 not begin a new cycle of treatment unless the ANC is $\geq 1500 \text{ cells/mm}^3$, the platelet count is
401 $\geq 100,000 \text{ cells/mm}^3$, and creatinine clearance is $\geq 45 \text{ mL/min}$. Periodic chemistry tests should be
402 performed to evaluate renal and hepatic function.

403 *Dose Reduction Recommendations* — Dose adjustments at the start of a subsequent cycle
404 should be based on nadir hematologic counts or maximum nonhematologic toxicity from the
405 preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery.
406 Upon recovery, patients should be retreated using the guidelines in Tables 8-10, which are
407 suitable for using ALIMTA as a single agent or in combination with cisplatin.

408

Table 8: Dose Reduction for ALIMTA (single-agent or in combination) and Cisplatin - Hematologic Toxicities

Nadir ANC $<500/\text{mm}^3$ and nadir platelets $\geq 50,000/\text{mm}^3$.	75% of previous dose (both drugs).
Nadir platelets $<50,000/\text{mm}^3$ regardless of nadir ANC.	50% of previous dose (both drugs).

409
410 If patients develop nonhematologic toxicities (excluding neurotoxicity) \geq Grade 3 (except
411 Grade 3 transaminase elevations), ALIMTA should be withheld until resolution to less than or
412 equal to the patient's pre-therapy value. Treatment should be resumed according to guidelines in
413 Table 9.
414

Table 9: Dose Reduction for ALIMTA (single-agent or in combination) and Cisplatin - Nonhematologic Toxicities^{a,b}

	Dose of ALIMTA (mg/m^2)	Dose of Cisplatin (mg/m^2)
Any Grade 3 ^c or 4 toxicities except mucositis	75% of previous dose	75% of previous dose
Any diarrhea requiring hospitalization (irrespective of Grade) or Grade 3 or 4 diarrhea	75% of previous dose	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose	100% of previous dose

415 ^a NCI Common Toxicity Criteria (CTC).

416 ^b Excluding neurotoxicity.

417 ^c Except Grade 3 transaminase elevation.
418

419 In the event of neurotoxicity, the recommended dose adjustments for ALIMTA and cisplatin
420 are described in Table 10. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is
421 experienced.
422

Table 10: Dose Reduction for ALIMTA (single-agent or in combination) and Cisplatin - Neurotoxicity

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

423
424 ALIMTA therapy should be discontinued if a patient experiences any hematologic or
425 nonhematologic Grade 3 or 4 toxicity after 2 dose reductions (except Grade 3 transaminase
426 elevations) or immediately if Grade 3 or 4 neurotoxicity is observed.

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

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

431 *Renally Impaired Patients* — In clinical studies, patients with creatinine clearance ≥ 45 mL/min
432 required no dose adjustments other than those recommended for all patients. Insufficient
433 numbers of patients with creatinine clearance below 45 mL/min have been treated to make
434 dosage recommendations for this group of patients. Therefore, ALIMTA should not be
435 administered to patients whose creatinine clearance is <45 mL/min using the standard Cockcroft
436 and Gault formula (below) or GFR measured by Tc99m-DPTA serum clearance method:

437

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

Females: Estimated creatinine clearance for males \times 0.85

438

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

442 *Hepatically Impaired Patients* — ALIMTA is not extensively metabolized by the liver. Dose
443 adjustments based on hepatic impairment experienced during treatment with ALIMTA are
444 provided in Table 9 (*see Patients with Hepatic Impairment under PRECAUTIONS*).

445 **Preparation and Administration Precautions**

446 As with other potentially toxic anticancer agents, care should be exercised in the handling and
447 preparation of infusion solutions of ALIMTA. The use of gloves is recommended. If a solution
448 of ALIMTA contacts the skin, wash the skin immediately and thoroughly with soap and water. If
449 ALIMTA contacts the mucous membranes, flush thoroughly with water. Several published
450 guidelines for handling and disposal of anticancer agents are available.¹⁻⁸ There is no general
451 agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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

456 **Preparation for Intravenous Infusion Administration**

- 457 1. Use aseptic technique during the reconstitution and further dilution of ALIMTA for
458 intravenous infusion administration.
- 459 2. Calculate the dose and the number of ALIMTA vials needed. Each vial contains 500 mg
460 of ALIMTA. The vial contains an excess of ALIMTA to facilitate delivery of label
461 amount.
- 462 3. Reconstitute 500-mg vials with 20 mL of 0.9% Sodium Chloride Injection (preservative
463 free) to give a solution containing 25 mg/mL ALIMTA. Gently swirl each vial until the
464 powder is completely dissolved. The resulting solution is clear and ranges in color from
465 colorless to yellow or green-yellow without adversely affecting product quality. The pH
466 of the reconstituted ALIMTA solution is between 6.6 and 7.8. **FURTHER DILUTION IS**
467 **REQUIRED.**
- 468 4. Parenteral drug products should be inspected visually for particulate matter and
469 discoloration prior to administration. If particulate matter is observed, do not administer.
- 470 5. The appropriate volume of reconstituted ALIMTA solution should be further diluted to
471 100 mL with 0.9% Sodium Chloride Injection (preservative free) and administered as an
472 intravenous infusion over 10 minutes.
- 473 6. Chemical and physical stability of reconstituted and infusion solutions of ALIMTA were
474 demonstrated for up to 24 hours following initial reconstitution, when stored at
475 refrigerated or ambient room temperature [see USP Controlled Room Temperature] and
476 lighting. When prepared as directed, reconstitution and infusion solutions of ALIMTA
477 contain no antimicrobial preservatives. Discard any unused portion.

478 Reconstitution and further dilution prior to intravenous infusion is only recommended with
479 0.9% Sodium Chloride Injection (preservative free). ALIMTA is physically incompatible with
480 diluents containing calcium, including Lactated Ringer's Injection, USP and Ringer's
481 Injection, USP and therefore these should not be used. Coadministration of ALIMTA with other
482 drugs and diluents has not been studied, and therefore is not recommended.

HOW SUPPLIED

483
 484 ALIMTA[®], pemetrexed for injection is available in sterile single-use vials containing 500 mg
 485 pemetrexed.
 486 NDC 0002-7623-01 (VL7623): single-use vial with flip-off cap individually packaged in a
 487 carton.

Storage

488
 489 ALIMTA, pemetrexed for injection, should be stored at 25°C (77°F); excursions permitted to
 490 15-30°C (59-86°F) [see USP Controlled Room Temperature].
 491 Chemical and physical stability of reconstituted and infusion solutions of ALIMTA were
 492 demonstrated for up to 24 hours following initial reconstitution, when stored refrigerated,
 493 2-8°C (36-46°F), or at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP
 494 Controlled Room Temperature]. When prepared as directed, reconstituted and infusion solutions
 495 of ALIMTA contain no antimicrobial preservatives. Discard unused portion.
 496 ALIMTA is not light sensitive.

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519 Literature revised January 9, 2006

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525
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527 **INFORMATION FOR PATIENTS AND CAREGIVERS**

528
529

ALIMTA[®] (uh-LIM-tuh) (pemetrexed for injection)

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

534 What is ALIMTA?

535 ALIMTA is a treatment for:

- 536 • **Malignant pleural mesothelioma.** This cancer affects the inside lining of the chest
537 cavity. ALIMTA is given with cisplatin, another anti-cancer medicine (chemotherapy).
- 538 • **Non-small cell lung cancer.** This cancer is a disease in which malignant (cancer) cells
539 form in the tissues of the lung.

540 **To lower your chances of side effects of ALIMTA, you must also take folic acid and**
541 **vitamin B₁₂ prior to and during your treatment with ALIMTA.** Your doctor will prescribe a
542 medicine called a “corticosteroid” to take for 3 days during your treatment with ALIMTA.
543 Corticosteroid medicines lower your chances of getting skin reactions with ALIMTA.

544 ALIMTA has not been studied in children.

545 What should I tell my doctor before taking ALIMTA?

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

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

556 How is ALIMTA given?

- 557 • ALIMTA is slowly infused (injected) into a vein. The injection or infusion will last about
558 10 minutes. You will usually receive ALIMTA once every 21 days (3 weeks).
- 559 • If you are being treated for malignant pleural mesothelioma, ALIMTA is given in
560 combination with cisplatin (another anti-cancer drug). Cisplatin is infused in your vein
561 for about 2 hours starting about 30 minutes after your treatment with ALIMTA.
- 562 • Your doctor will prescribe a medicine called a “corticosteroid” to take for 3 days during
563 your treatment with ALIMTA. Corticosteroid medicines lower your chances for getting
564 skin reactions with ALIMTA.
- 565 • **It is very important to take folic acid and vitamin B₁₂ during your treatment with**
566 **ALIMTA to lower your chances of harmful side effects.** You must start taking

567 350-1000 micrograms of folic acid every day for at least 5 days out of the 7 days before
 568 your first dose of ALIMTA. You must keep taking folic acid every day during the time
 569 you are getting treatment with ALIMTA, and for 21 days after your last treatment. You
 570 can get folic acid vitamins over-the-counter. Folic acid is also found in many
 571 multivitamin pills. Ask your doctor or pharmacist for help if you are not sure how to
 572 choose a folic acid product. Your doctor will give you vitamin B₁₂ injections while you
 573 are getting treatment with ALIMTA. You will get your first vitamin B₁₂ injection during
 574 the week before your first dose of ALIMTA, and then about every 9 weeks during
 575 treatment.

- 576 • You will have regular blood tests before and during your treatment with ALIMTA. Your
 577 doctor may adjust your dose of ALIMTA or delay treatment based on the results of your
 578 blood tests and on your general condition.

579 **What should I avoid while taking ALIMTA?**

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

585 **What are the possible side effects of ALIMTA?**

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

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

- 592 • **Stomach upset, including nausea, vomiting, and diarrhea.** You can obtain medicines
 593 to help control some of these symptoms. Call your doctor if you get any of these
 594 symptoms.
- 595 • **Low blood cell counts:**
 - 596 • **Low red blood cells.** Low red blood cells may make you feel tired, get tired
 597 easily, appear pale, and become short of breath.
 - 598 • **Low white blood cells.** Low white blood cells may give you a greater chance for
 599 infection. If you have a fever (temperature above 100.4°F) or other signs of
 600 infection, call your doctor right away.
 - 601 • **Low platelets.** Low platelets give you a greater chance for bleeding. Your doctor
 602 will do blood tests to check your blood counts before and during treatment with
 603 ALIMTA.
- 604 • **Tiredness.** You may feel tired or weak for a few days after your ALIMTA treatments. If
 605 you have severe weakness or tiredness, call your doctor.
- 606 • **Mouth, throat, or lip sores** (stomatitis, pharyngitis). You may get redness or sores in
 607 your mouth, throat, or on your lips. These symptoms may happen a few days after
 608 ALIMTA treatment. Talk with your doctor about proper mouth and throat care.
- 609 • **Loss of appetite.** You may lose your appetite and lose weight during your treatment.
 610 Talk to your doctor if this is a problem for you.

611 • **Rash.** You may get a rash or itching during treatment. These usually appear between
612 treatments with ALIMTA and usually go away before the next treatment. Call your
613 doctor if you get a severe rash or itching.

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

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

618 **General information about ALIMTA**

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

621 This leaflet summarizes the most important information about ALIMTA. If you would like more
622 information, talk with your doctor. You can ask your doctor or pharmacist for information about
623 ALIMTA that is written for health professionals. You can also call 1-800-LILLY-RX
624 (1-800-545-5979) or visit www.ALIMTA.com.

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BB30

Exp. Date / Control No.

ALIMTA[®]
pemetrexed
for injection

Single-Use Vial
NDC 0002-7623-01
VL7623

FC 5280 AMS
FC 5280 AMS
FC 5280 AMS

Single-Use Vial
NDC 0002-7623-01
VL7623

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pemetrexed
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pemetrexed
for injection

ALIMTA[®]
pemetrexed
for injection



3 0002-7623-01 6

Eli Lilly and Company
Indianapolis, IN 46285, USA

Each vial contains pemetrexed disodium equivalent to 500 mg pemetrexed, 500 mg of mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

To Reconstitute: Add 20 mL of 0.9% Sodium Chloride Injection (preservative free) to make a solution containing 25 mg/mL pemetrexed. Reconstituted solution must be further diluted before use (see accompanying literature).

Administer infusion solution within 24 hours after initial reconstitution. Discard unused portion.

See accompanying literature for dosage.

500 mg

For intravenous use only.

Rx only

www.ALIMTA.com

Storage: Store powder at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Store reconstituted and infusion solutions at refrigerated, 2-8°C (36-46°F), or 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Caution: Cytotoxic Agent

FC 5280 AMS

Single-Use Vial
NDC 0002-7623-01
VL7623

ALIMTA[®]
pemetrexed
for injection

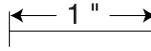
C-1057

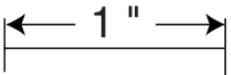
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3



ALIMTA[®]
pemetrexed
for injection

500 mg

For intravenous use only.

Rx only

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Single-Use Vial NDC 0002-7623-01
VL7623

Caution: Cytotoxic Agent

Each vial contains pemetrexed disodium equivalent to 500 mg pemetrexed, 500 mg of mannitol, Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

Storage: Store powder at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. See accompanying literature for storage of reconstituted and infusion solutions.

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● **WX 1000 AMX** ●

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