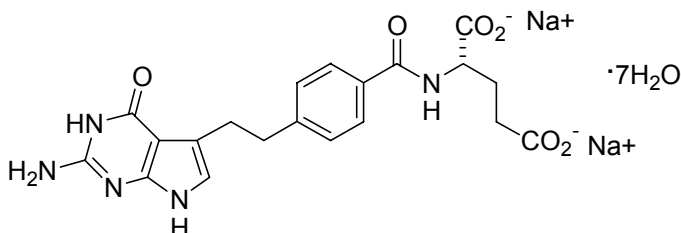


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**ALIMTA<sup>®</sup>**  
**pemetrexed**  
**for injection**

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**DESCRIPTION**

7 ALIMTA<sup>®</sup>, pemetrexed for injection, is an antifolate antineoplastic agent that exerts its action  
8 by disrupting folate-dependent metabolic processes essential for cell replication. Pemetrexed  
9 disodium heptahydrate has the chemical name L-Glutamic acid, *N*-[4-[2-(2-amino-4,7-dihydro-4-  
10 oxo-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate. It is a white  
11 to almost-white solid with a molecular formula of C<sub>20</sub>H<sub>19</sub>N<sub>5</sub>Na<sub>2</sub>O<sub>6</sub>•7H<sub>2</sub>O and a molecular weight



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 folyl polyglutamate synthase. 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 B<sub>12</sub> supplementation were characterized using  
36 population pharmacodynamic analyses. Severity of hematologic toxicity, as measured by the  
37 depth of the ANC nadir, is inversely proportional to the systemic exposure of ALIMTA. It was  
38 also 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 B<sub>12</sub> 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  
44 4.2 to 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  $\text{mg}/\text{m}^2$  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  $\text{mL}/\text{min}$  and the elimination half-life of pemetrexed is 3.5 hours in patients with normal  
52 renal function (creatinine clearance of 90  $\text{mL}/\text{min}$ ). The clearance decreases, and exposure  
53 (AUC) increases, as renal function decreases. Pemetrexed total systemic exposure (AUC) and  
54 maximum plasma concentration ( $C_{\text{max}}$ ) increase proportionally with dose. The pharmacokinetics  
55 of pemetrexed do not change over multiple treatment cycles. Pemetrexed has a steady-state  
56 volume of distribution of 16.1 liters. In vitro studies indicate that pemetrexed is approximately  
57 81% bound to plasma proteins. Binding is not affected by degree of renal impairment.

#### 58 **Drug Interactions**

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

61 *Vitamins* — Coadministration of oral folic acid or intramuscular vitamin B<sub>12</sub> does not affect the  
62 pharmacokinetics of pemetrexed.

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

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

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

#### 76 **Special Populations**

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

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

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

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

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

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

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

### 96 **CLINICAL STUDIES**

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

100 Randomized Trial: A multi-center, randomized, single-blind study in 448 chemo-naïve patients  
101 with MPM compared survival in patients treated with ALIMTA in combination with cisplatin to  
102 survival in patients receiving cisplatin alone. ALIMTA was administered intravenously over  
103 10 minutes at a dose of 500 mg/m<sup>2</sup> and cisplatin was administered intravenously over 2 hours at  
104 a dose of 75 mg/m<sup>2</sup> beginning approximately 30 minutes after the end of administration of  
105 ALIMTA. Both drugs were given on Day 1 of each 21-day cycle. After 112 patients were  
106 treated, white cell and GI toxicity led to a change in protocol whereby all patients were given  
107 folic acid and vitamin B<sub>12</sub> supplementation.

108 The primary analysis of this study was performed on the population of all patients randomly  
109 assigned to treatment who received study drug (randomized and treated). An analysis was also  
110 performed on patients who received folic acid and vitamin B<sub>12</sub> supplementation during the entire  
111 course of study therapy (fully supplemented), as supplementation is recommended (*see* Dosage  
112 and Administration). Results in all patients and those fully supplemented were similar. Patient  
113 demographics are shown in Table 1.

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115

**Table 1: Summary of Patient Characteristics**

Patient characteristic	Randomized and Treated Patients		Fully Supplemented Patients	
	ALIMTA/cis (N=226)	Cisplatin (N=222)	ALIMTA/cis (N=168)	Cisplatin (N=163)
<b>Age (yrs)</b>				
Median (range)	61 (29-85)	60 (19-84)	60 (29-85)	60 (19-82)
<b>Gender (%)</b>				
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)
<b>Origin (%)</b>				
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
<b>Stage at Entry (%)</b>				
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)

<b>Diagnosis/ Histology<sup>a</sup> (%)</b>				
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)
<b>Baseline KPS<sup>b</sup> (%)</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)

<sup>a</sup> Only 67% of the patients had the histologic diagnosis of malignant mesothelioma confirmed by independent review.

<sup>b</sup> Karnofsky Performance Scale.

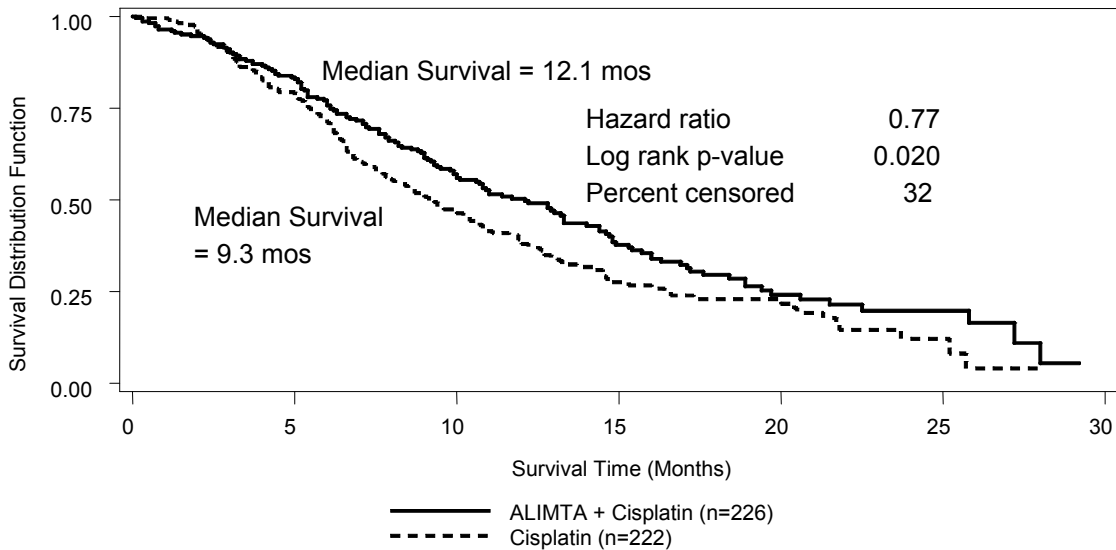
Table 2 summarizes the survival results for all randomized and treated patients regardless of vitamin supplementation status and those patients receiving vitamin supplementation from the time of enrollment in the trial.

**Table 2: Efficacy of ALIMTA plus Cisplatin vs. Cisplatin  
in Malignant Pleural Mesothelioma**

Efficacy Parameter	Randomized and Treated Patients		Fully Supplemented Patients	
	ALIMTA/cis (N=226)	Cisplatin (N=222)	ALIMTA/cis (N=168)	Cisplatin (N=163)
Median overall survival (95% CI)	12.1 mos (10.0-14.4)	9.3 mos (7.8-10.7)	13.3 mos (11.4-14.9)	10.0 mos (8.4-11.9)
Hazard ratio	0.77		0.75	
Log rank p-value*	0.020		0.051	

\* p-value refers to comparison between arms.

Similar results were seen in the analysis of patients (N=303) with confirmed histologic diagnosis of malignant pleural mesothelioma. Exploratory demographic analyses showed no apparent differences in patients over or under 65. There were too few non-white patients to assess possible ethnic differences. The effect in women (median survival 15.7 months with the combination vs 7.5 months on cisplatin alone), however, was larger than the effect in males (median survival 11 vs 9.4 respectively). As with any exploratory analysis, it is not yet clear whether this difference is real or is a chance finding.



134  
135 **Figure 1: Kaplan-Meier Estimates of Survival Time for ALIMTA plus**  
136 **Cisplatin and Cisplatin Alone in all Randomized and Treated Patients.**  
137

138 Objective tumor response for malignant pleural mesothelioma is difficult to measure and  
139 response criteria are not universally agreed upon. However, based upon prospectively defined  
140 criteria, the objective tumor response rate for ALIMTA plus cisplatin was greater than the  
141 objective tumor response rate for cisplatin alone. There was also improvement in lung function  
142 (forced vital capacity) in the ALIMTA plus cisplatin arm compared to the control arm.  
143

144 Patients who received full supplementation with folic acid and vitamin B<sub>12</sub> during study  
145 therapy received a median of 6 and 4 cycles in the ALIMTA/cisplatin (N=168) and cisplatin  
146 (N=163) arms, respectively. Patients who never received folic acid and vitamin B<sub>12</sub> during study  
147 therapy received a median of 2 cycles in both treatment arms (N=32 and N=38 for the  
148 ALIMTA/cisplatin and cisplatin arm, respectively). Patients receiving ALIMTA in the fully  
149 supplemented group received a relative dose intensity of 93% of the protocol specified ALIMTA  
150 dose intensity; patients treated with cisplatin in the same group received 94% of the projected  
151 dose intensity. Patients treated with cisplatin alone had a dose intensity of 96%.

#### 152 **INDICATIONS AND USAGE**

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

#### 156 **CONTRAINDICATIONS**

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

#### 159 **WARNINGS**

##### 160 **Decreased Renal Function**

161 ALIMTA is primarily eliminated unchanged by renal excretion. No dosage adjustment is  
162 needed in patients with creatinine clearance  $\geq 45$  mL/min. Insufficient numbers of patients have  
163 been studied with creatinine clearance  $< 45$  mL/min to give a dose recommendation. Therefore,  
164 ALIMTA should not be administered to patients whose creatinine clearance is  $< 45$  mL/min (*see*  
165 **Dose Reduction Recommendations under DOSAGE AND ADMINISTRATION**).

166 One patient with severe renal impairment (creatinine clearance 19 mL/min) who did not  
167 receive folic acid and vitamin B<sub>12</sub> died of drug-related toxicity following administration of  
168 ALIMTA alone.

### 169 **Bone Marrow Suppression**

170 ALIMTA can suppress bone marrow function, manifested by neutropenia, thrombocytopenia,  
171 and anemia (*see ADVERSE REACTIONS*); myelosuppression is usually the dose-limiting  
172 toxicity. Dose reductions for subsequent cycles are based on nadir ANC, platelet count, and  
173 maximum nonhematologic toxicity seen in the previous cycle (*see Dose Reduction*  
174 *Recommendations under DOSAGE AND ADMINISTRATION*).

### 175 **Need for Folate and Vitamin B<sub>12</sub> Supplementation**

176 Patients treated with ALIMTA must be instructed to take folic acid and vitamin B<sub>12</sub> as a  
177 prophylactic measure to reduce treatment-related hematologic and GI toxicity (*see DOSAGE*  
178 *AND ADMINISTRATION*). In clinical studies, less overall toxicity and reductions in  
179 Grade 3/4 hematologic and nonhematologic toxicities such as neutropenia, febrile neutropenia,  
180 and infection with Grade 3/4 neutropenia were reported when pretreatment with folic acid and  
181 vitamin B<sub>12</sub> was administered.

### 182 **Pregnancy Category D**

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

## 193 **PRECAUTIONS**

### 194 **General**

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

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

### 205 **Laboratory Tests**

206 Complete blood cell counts, including platelet counts and periodic chemistry tests, should be  
207 performed on all patients receiving ALIMTA. Patients should be monitored for nadir and  
208 recovery, which were tested in the clinical study before each dose and on days 8 and 15 of each  
209 cycle. Patients should not begin a new cycle of treatment unless the ANC is  $\geq 1500$  cells/mm<sup>3</sup>,  
210 the platelet count is  $\geq 100,000$  cells/mm<sup>3</sup>, and creatinine clearance is  $\geq 45$  mL/min.



211 **Drug Interactions**

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

216 Although ibuprofen (400 mg qid) can be administered with ALIMTA in patients with normal  
217 renal function (creatinine clearance  $\geq 80$  mL/min), caution should be used when administering  
218 ibuprofen concurrently with ALIMTA to patients with mild to moderate renal insufficiency  
219 (creatinine clearance from 45 to 79 mL/min). Patients with mild to moderate renal insufficiency  
220 should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the  
221 day of, and 2 days following administration of ALIMTA.

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

227 **Drug/Laboratory Test Interactions**

228 None known.

229 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

230 No carcinogenicity studies have been conducted with pemetrexed. Pemetrexed was clastogenic  
231 in the in vivo micronucleus assay in mouse bone marrow but was not mutagenic in multiple  
232 in vitro tests (Ames assay, CHO cell assay). Pemetrexed administered at i.v. doses of  
233 0.1 mg/kg/day or greater to male mice (about 1/1666 the recommended human dose-on a  $\text{mg}/\text{m}^2$   
234 basis) resulted in reduced fertility, hypospermia, and testicular atrophy.

235 **Pregnancy**

236 Pregnancy Category D (*see* WARNINGS).

237 **Nursing Mothers**

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

242 **Pediatric Use**

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

244 **Geriatric Use**

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

248 **Gender**

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

252 **Patients with Hepatic Impairment**

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

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

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

261 **Patients with Renal Impairment**

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

267 **ADVERSE REACTIONS**

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

**Table 3: Adverse Events\* in Fully Supplemented Patients Receiving ALIMTA plus  
Cisplatin in MPM  
CTC Grades (% incidence)**

	All Reported Adverse Events Regardless of Causality					
	ALIMTA/cis (N=168)			Cisplatin (N=163)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
<b>Laboratory</b>						
<b>Hematologic</b>						
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
<b>Renal</b>						
Creatinine elevation	16	1	0	12	1	0
Renal failure	2	0	1	1	0	0
<b>Clinical</b>						
<b>Constitutional Symptoms</b>						
Fatigue	80	17	0	74	12	1
Fever	17	0	0	9	0	0
Other constitutional symptoms	11	2	1	8	1	1
<b>Cardiovascular General</b>						
Thrombosis/embolism	7	4	2	4	3	1
<b>Gastrointestinal</b>						



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
<b>Pulmonary</b>						
Dyspnea	66	10	1	62	5	2
<b>Pain</b>						
Chest pain	40	8	1	30	5	1
<b>Neurology</b>						
Neuropathy/sensory	17	0	0	15	1	0
Mood alteration/depression	14	1	0	9	1	0
<b>Infection/Febrile Neutropenia</b>						
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
<b>Immune</b>						
Allergic reaction/hypersensitivity	2	0	0	1	0	0
<b>Dermatology/Skin</b>						
Rash/desquamation	22	1	0	9	0	0

\* Refer to NCI CTC Version 2.0.

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Table 4 compares the incidence (percentage of patients) of CTC Grade 3/4 toxicities in patients who received vitamin supplementation with daily folic acid and vitamin B<sub>12</sub> from the time of enrollment in the study (fully supplemented) with the incidence in patients who never received vitamin supplementation (never supplemented) during the study in the ALIMTA plus cisplatin arm.

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

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

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<sup>a</sup> Refer to NCI CTC criteria for lab and non-laboratory values for each grade of toxicity (version 2.0).

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

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

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### OVERDOSAGE

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

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In clinical trials, leucovorin was permitted for CTC Grade 4 leukopenia lasting  $\geq 3$  days, CTC Grade 4 neutropenia lasting  $\geq 3$  days, and immediately for CTC Grade 4 thrombocytopenia, bleeding associated with Grade 3 thrombocytopenia, or Grade 3 or 4 mucositis. The following intravenous doses and schedules of leucovorin were recommended for intravenous use: 100 mg/m<sup>2</sup>, intravenously once, followed by leucovorin, 50 mg/m<sup>2</sup>, intravenously every 6 hours for 8 days.

304

The ability of ALIMTA to be dialyzed is unknown.

305  
306

## DOSAGE AND ADMINISTRATION

### ALIMTA is for Intravenous Infusion Only

#### 307 **Combination Use With Cisplatin**

308 *Malignant Pleural Mesothelioma* — The recommended dose of ALIMTA is 500 mg/m<sup>2</sup>  
309 administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle. The  
310 recommended dose of cisplatin is 75 mg/m<sup>2</sup> infused over 2 hours beginning approximately  
311 30 minutes after the end of ALIMTA administration. Patients should receive hydration consistent  
312 with local practice prior to and/or after receiving cisplatin. See cisplatin package insert for more  
313 information.

#### 314 **Premedication Regimen**

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

319 *Vitamin Supplementation* — To reduce toxicity, patients treated with ALIMTA must be  
320 instructed to take a low-dose oral folic acid preparation or multivitamin with folic acid on a daily  
321 basis. At least 5 daily doses of folic acid must be taken during the 7-day period preceding the  
322 first dose of ALIMTA; and dosing should continue during the full course of therapy and for  
323 21 days after the last dose of ALIMTA. Patients must also receive one (1) intramuscular  
324 injection of vitamin B<sub>12</sub> during the week preceding the first dose of ALIMTA and every 3 cycles  
325 thereafter. Subsequent vitamin B<sub>12</sub> injections may be given the same day as ALIMTA. In clinical  
326 trials, the dose of folic acid studied ranged from 350 to 1000 µg, and the dose of vitamin B<sub>12</sub> was  
327 1000 µg. The most commonly used dose of oral folic acid in clinical trials was 400 µg (*see*  
328 **WARNINGS**).

#### 329 **Laboratory Monitoring and Dose Reduction Recommendations**

330 *Monitoring* — Complete blood cell counts, including platelet counts, should be performed on  
331 all patients receiving ALIMTA. Patients should be monitored for nadir and recovery, which were  
332 tested in the clinical study before each dose and on days 8 and 15 of each cycle. Patients should  
333 not begin a new cycle of treatment unless the ANC is ≥1500 cells/mm<sup>3</sup>, the platelet count is  
334 ≥100,000 cells/mm<sup>3</sup>, and creatinine clearance is ≥45 mL/min. Periodic chemistry tests should be  
335 performed to evaluate renal and hepatic function.

336 *Dose Reduction Recommendations* — Dose adjustments at the start of a subsequent cycle  
337 should be based on nadir hematologic counts or maximum nonhematologic toxicity from the  
338 preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery.  
339 Upon recovery, patients should be retreated using the guidelines in Tables 5-7.

340

**Table 5: Dose Reduction for ALIMTA and Cisplatin - Hematologic Toxicities**

Nadir ANC <500/mm <sup>3</sup> and nadir platelets ≥50,000/mm <sup>3</sup> .	75% of previous dose (both drugs).
Nadir platelets <50,000/mm <sup>3</sup> regardless of nadir ANC.	50% of previous dose (both drugs).

341

342 If patients develop nonhematologic toxicities (excluding neurotoxicity) ≥Grade 3 (except  
343 Grade 3 transaminase elevations), ALIMTA should be withheld until resolution to less than or  
344 equal to the patient's pre-therapy value. Treatment should be resumed according to guidelines in  
345 Table 6.

346

**Table 6: Dose Reduction - Nonhematologic Toxicities<sup>a,b</sup>**

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

347 <sup>a</sup> NCI Common Toxicity Criteria (CTC).

348 <sup>b</sup> Excluding neurotoxicity.

349 <sup>c</sup> Except Grade 3 transaminase elevation.

350

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

354

**Table 7: Dose Reduction for ALIMTA and Cisplatin - Neurotoxicity**

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

355

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

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

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

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

369

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

Females: Estimated creatinine clearance for males × 0.85

370

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

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

### 377 **Preparation and Administration Precautions**

378 As with other potentially toxic anticancer agents, care should be exercised in the handling and  
379 preparation of infusion solutions of ALIMTA. The use of gloves is recommended. If a solution

380 of ALIMTA contacts the skin, wash the skin immediately and thoroughly with soap and water. If  
381 ALIMTA contacts the mucous membranes, flush thoroughly with water. Several published  
382 guidelines for handling and disposal of anticancer agents are available.<sup>1-8</sup> There is no general  
383 agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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

### 388 **Preparation for Intravenous Infusion Administration**

- 389 1. Use aseptic technique during the reconstitution and further dilution of ALIMTA for  
390 intravenous infusion administration.
- 391 2. Calculate the dose and the number of ALIMTA vials needed. Each vial contains 500 mg  
392 of ALIMTA. The vial contains an excess of ALIMTA to facilitate delivery of label  
393 amount.
- 394 3. Reconstitute 500-mg vials with 20 mL of 0.9% Sodium Chloride Injection (preservative  
395 free) to give a solution containing 25 mg/mL ALIMTA. Gently swirl each vial until the  
396 powder is completely dissolved. The resulting solution is clear and ranges in color from  
397 colorless to yellow or green-yellow without adversely affecting product quality. The pH  
398 of the reconstituted ALIMTA solution is between 6.6 and 7.8. FURTHER DILUTION IS  
399 REQUIRED.
- 400 4. Parenteral drug products should be inspected visually for particulate matter and  
401 discoloration prior to administration. If particulate matter is observed, do not administer.
- 402 5. The appropriate volume of reconstituted ALIMTA solution should be further diluted to  
403 100 mL with 0.9% Sodium Chloride Injection (preservative free) and administered as an  
404 intravenous infusion over 10 minutes.
- 405 6. Chemical and physical stability of reconstituted and infusion solutions of ALIMTA were  
406 demonstrated for up to 24 hours following initial reconstitution, when stored at  
407 refrigerated or ambient room temperature [see USP Controlled Room Temperature] and  
408 lighting. When prepared as directed, reconstitution and infusion solutions of ALIMTA  
409 contain no antimicrobial preservatives. Discard any unused portion.

410 Reconstitution and further dilution prior to intravenous infusion is only recommended with  
411 0.9% Sodium Chloride Injection (preservative free). ALIMTA is physically incompatible with  
412 diluents containing calcium, including Lactated Ringer's Injection, USP and Ringer's Injection,  
413 USP and therefore these should not be used. Coadministration of ALIMTA with other drugs and  
414 diluents has not been studied, and therefore is not recommended.

### 415 **HOW SUPPLIED**

416 ALIMTA<sup>®</sup>, pemetrexed for injection is available in sterile single-use vials containing 500 mg  
417 pemetrexed.

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

### 420 **Storage**

421 ALIMTA, pemetrexed for injection, should be stored at 25°C (77°F); excursions permitted to  
422 15-30°C (59-86°F) [see USP Controlled Room Temperature].

423 Chemical and physical stability of reconstituted and infusion solutions of ALIMTA were  
424 demonstrated for up to 24 hours following initial reconstitution, when stored refrigerated, 2-8°C  
425 (36-46°F), or at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled  
426 Room Temperature]. When prepared as directed, reconstituted and infusion solutions of  
427 ALIMTA contain no antimicrobial preservatives. Discard unused portion.

428 ALIMTA is not light sensitive.

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