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ALIMTA[®]

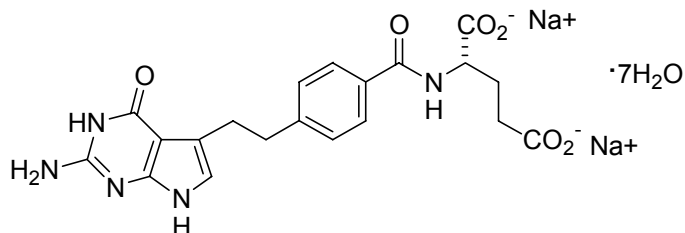
pemetrexed

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 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 B₁₂ 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 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
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 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 exposure
53 (AUC) increases, as renal function decreases. Pemetrexed total systemic exposure (AUC) and
54 maximum plasma concentration (C_{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 B₁₂ 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/m² and cisplatin was administered intravenously over 2 hours at
 104 a dose of 75 mg/m² 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 B₁₂ 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 B₁₂ 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.

114
 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) |
| Age (yrs) | | | | |
| Median (range) | 61 (29-85) | 60 (19-84) | 60 (29-85) | 60 (19-82) |
| Gender (%) | | | | |
| Male | 184 (81.4) | 181 (81.5) | 136 (81.0) | 134 (82.2) |
| Female | 42 (18.6) | 41 (18.5) | 32 (19.0) | 29 (17.8) |
| Origin (%) | | | | |
| Caucasian | 204 (90.3) | 206 (92.8) | 150 (89.3) | 153 (93.9) |
| Hispanic | 11 (4.9) | 12 (5.4) | 10 (6.0) | 7 (4.3) |
| Asian | 10 (4.4) | 4 (1.9) | 7 (4.2) | 3 (1.8) |
| African descent | 1 (0.4) | 0 | 1 (0.6) | 0 |
| Stage at Entry (%) | | | | |
| I | 16 (7.1) | 14 (6.3) | 15 (8.9) | 12 (7.4) |
| II | 35 (15.6) | 33 (15.0) | 27 (16.2) | 27 (16.8) |
| III | 73 (32.4) | 68 (30.6) | 51 (30.5) | 49 (30.4) |
| IV | 101 (44.9) | 105 (47.2) | 74 (44.3) | 73 (45.3) |
| Unspecified | 1 (0.4) | 2 (0.9) | 1 (0.6) | 2 (1.2) |

| Diagnosis/ Histology^a (%) | | | | |
|---|------------|------------|------------|------------|
| Epithelial | 154 (68.1) | 152 (68.5) | 117 (69.6) | 113 (69.3) |
| Mixed | 37 (16.4) | 36 (16.2) | 25 (14.9) | 25 (15.3) |
| Sarcomatoid | 18 (8.0) | 25 (11.3) | 14 (8.3) | 17 (10.4) |
| Other | 17 (7.5) | 9 (4.1) | 12 (7.1) | 8 (4.9) |
| Baseline KPS^b (%) | | | | |
| 70-80 | 109 (48.2) | 97 (43.7) | 83 (49.4) | 69 (42.3) |
| 90-100 | 117 (51.8) | 125 (56.3) | 85 (50.6) | 94 (57.7) |

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

^b Karnofsky Performance Scale.

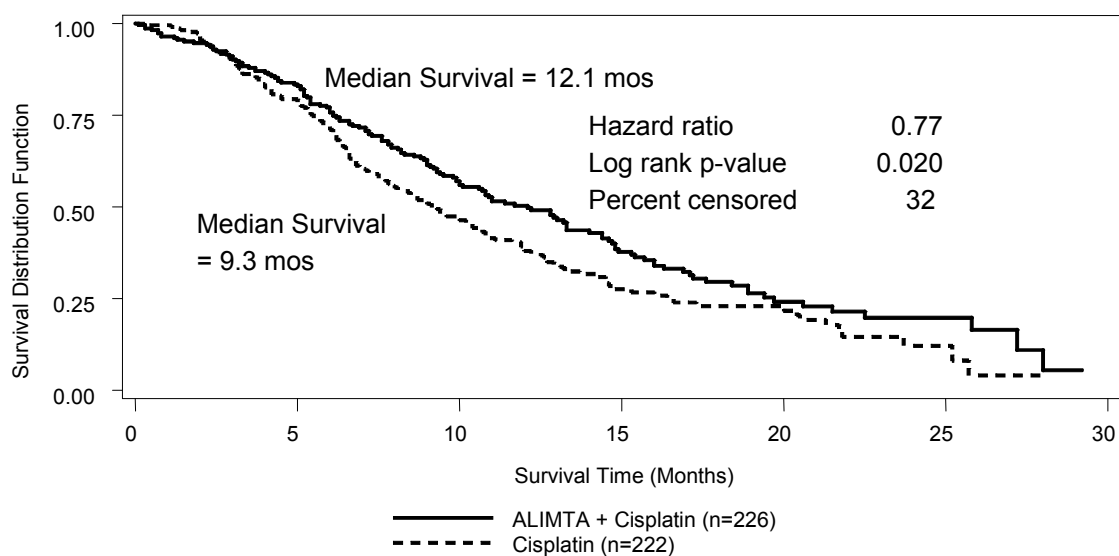
Table 2 summarizes the survival results for all randomized and treated patients regardless of vitamin supplementation status and those patients receiving vitamin supplementation from the time of enrollment in the trial.

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

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

* p-value refers to comparison between arms.

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



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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.

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 B₁₂ 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 B₁₂ 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 ≥ 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 B₁₂ 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 B₁₂ Supplementation**

176 Patients treated with ALIMTA must be instructed to take folic acid and vitamin B₁₂ 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 B₁₂ 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/m²) or 5 mg/kg (15 mg/m²)
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/m² basis), and cleft palate at 5 mg/kg (about 1/33 the recommended i.v. human dose on
188 a mg/m² 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 ≥ 1500 cells/mm³,
210 the platelet count is $\geq 100,000$ cells/mm³, and creatinine clearance is ≥ 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 ≥ 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 mg/m²
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 |
| 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.

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274
275 Table 4 compares the incidence (percentage of patients) of CTC Grade 3/4 toxicities in patients
276 who received vitamin supplementation with daily folic acid and vitamin B₁₂ from the time of
277 enrollment in the study (fully supplemented) with the incidence in patients who never received
278 vitamin supplementation (never supplemented) during the study in the ALIMTA plus
279 cisplatin arm.

280

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

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

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

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

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

291

OVERDOSAGE

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

298 In clinical trials, leucovorin was permitted for CTC Grade 4 leukopenia lasting ≥ 3 days, CTC
299 Grade 4 neutropenia lasting ≥ 3 days, and immediately for CTC Grade 4 thrombocytopenia,
300 bleeding associated with Grade 3 thrombocytopenia, or Grade 3 or 4 mucositis. The following
301 intravenous doses and schedules of leucovorin were recommended for intravenous use: 100
302 mg/m², intravenously once, followed by leucovorin, 50 mg/m², intravenously every 6 hours for 8
303 days.

304 The ability of ALIMTA to be dialyzed is unknown.

DOSAGE AND ADMINISTRATION
ALIMTA is for Intravenous Infusion Only

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306

307 **Combination Use With Cisplatin**

308 *Malignant Pleural Mesothelioma* — The recommended dose of ALIMTA is 500 mg/m²
 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/m² 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 B₁₂ during the week preceding the first dose of ALIMTA and every 3 cycles
 325 thereafter. Subsequent vitamin B₁₂ 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 B₁₂ 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/mm³, the platelet count is
 334 ≥100,000 cells/mm³, 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 ³ and nadir platelets ≥50,000/mm ³ . | 75% of previous dose (both drugs). |
| Nadir platelets <50,000/mm ³ regardless of nadir ANC. | 50% of previous dose (both drugs). |

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^{a,b}

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

^a NCI Common Toxicity Criteria (CTC).

^b Excluding neurotoxicity.

^c Except Grade 3 transaminase elevation.

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

Table 7: Dose Reduction for ALIMTA and Cisplatin - Neurotoxicity

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

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

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

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

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

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

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

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

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

Preparation and Administration Precautions

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

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.¹⁻⁸ 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[®], 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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