HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ALIMTA safely and effectively. See full prescribing information for ALIMTA.

ALIMTA (pemetrexed for injection), for Intravenous Use

Initial U.S. Approval: 2004

---------- RECENT MAJOR CHANGES ----------

Indications and Usage (1.1)	06/2018
Dosage and Administration (2.1)	06/2018

---------- INDICATIONS AND USAGE ----------

ALIMTA® is a folate analog metabolic inhibitor indicated:

- in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, non-small cell lung cancer (NSCLC). (1.1)
- in combination with carboplatin and pembrolizumab for the initial treatment of patients with metastatic, non-squamous NSCLC. This indication is approved under accelerated approval based on tumor response rate and progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.1)
- as a single agent for the maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. (1.1)
- as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy. (1.1)

Limitations of Use: ALIMTA is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer. (1.1)

- initial treatment, in combination with cisplatin, of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery. (1.2)

----------DOSAGE AND ADMINISTRATION----------

- The recommended dose of ALIMTA, administered as a single agent or with cisplatin or with carboplatin and pembrolizumab, in patients with creatinine clearance of 45 mL/minute or greater, is 500 mg/m^2 as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle. (2.1, 2.2)
- Initiate folic acid 400 mcg to 1000 mcg orally, once daily, beginning 7 days prior to the first dose of ALIMTA and continue until 21 days after the last dose of ALIMTA. (2.4)
- Administer vitamin B_{12}, 1 mg intramuscularly, 1 week prior to the first dose of ALIMTA and every 3 cycles. (2.4)
- Administer dexamethasone 4 mg orally, twice daily the day before, the day of, and the day after ALIMTA administration. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

For Injection: 100 mg or 500 mg lyophilized powder in single-dose vial. (3)

---------- CONTRAINDICATIONS ----------

History of severe hypersensitivity reaction to pemetrexed. (4)

----------WARNINGS AND PRECAUTIONS----------

- Myelosuppression: Can cause severe bone marrow suppression resulting in cytopenia and an increased risk of infection. Do not administer ALIMTA when the absolute neutrophil count is less than 1500 cells/mm^3 and platelets are less than 100,000 cells/mm^3. Initiate supplementation with oral folic acid and intramuscular vitamin B_{12} to reduce the severity of hematologic and gastrointestinal toxicity of ALIMTA. (2.6, 5.1)
- Renal Failure: Can cause severe, and sometimes fatal, renal failure. Do not administer when creatinine clearance is less than 45 mL/min. (2.3, 5.2)
- Bullous and Exfoliative Skin Toxicity: Permanently discontinue for severe and life-threatening bullous, blistering or exfoliating skin toxicity. (5.3)
- Interstitial Pneumonitis: Withhold for acute onset of new or progressive unexplained pulmonary symptoms. Permanently discontinue if pneumonitis is confirmed. (5.4)
- Radiation Recall: Can occur in patients who received radiation weeks to years previously; permanently discontinue for signs of radiation recall. (5.5)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of the potential risk to a fetus and to use effective contraception. (5.7, 8.1, 8.3)

----------ADVERSE REACTIONS----------

- The most common adverse reactions (incidence ≥20%) of ALIMTA, when administered as a single agent are fatigue, nausea, and anorexia. (6.1)
- The most common adverse reactions (incidence ≥20%) of ALIMTA when administered with cisplatin are vomiting, neutropenia, anemia, stomatitis/pharyngitis, thrombocytopenia, and constipation. (6.1)
- The most common adverse reactions (incidence ≥30%) of ALIMTA when administered in combination with carboplatin and pembrolizumab are fatigue, nausea, constipation, rash, vomiting, dyspnea, diarrhea, headache, and decreased appetite.

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

Ibuprofen increased risk of ALIMTA toxicity in patients with mild to moderate renal impairment. Modify the ibuprofen dosage as recommended for patients with a creatinine clearance between 45 mL/min and 79 mL/min. (2.5, 5.6, 7)

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

ALIMTA® is indicated:

- in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, non-small cell lung cancer (NSCLC).
- in combination with carboplatin and pembrolizumab for the initial treatment of patients with metastatic, non-squamous NSCLC. This indication is approved under accelerated approval based on tumor response rate and progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- as a single agent for the maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.
- as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy.

Limitations of Use: ALIMTA is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer *[see Clinical Studies 14.1].*

1.2 Mesothelioma

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Non-Squamous NSCLC

- The recommended dose of ALIMTA when administered with cisplatin for initial treatment of NSCLC in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m^2 as an intravenous infusion over 10 minutes administered prior to cisplatin on Day 1 of each 21-day cycle for up to six cycles in the absence of disease progression or unacceptable toxicity.

- The recommended dose of ALIMTA for maintenance treatment of NSCLC in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m^2 as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity after four cycles of platinum-based first-line chemotherapy.

- The recommended dose of ALIMTA for treatment of recurrent NSCLC in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m^2 as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity.

- The recommended dose of ALIMTA when administered with carboplatin and pembrolizumab for the initial treatment of NSCLC in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m^2 administered as an intravenous infusion over 10 minutes prior to carboplatin on Day 1 of each 21-day cycle for

alone or with pembrolizumab, until disease progression or unacceptable toxicity. Pembrolizumab should be administered prior to ALIMTA when given on the same day. Please refer to the full prescribing information for pembrolizumab and for carboplatin.

2.2 Recommended Dosage for Mesothelioma

- The recommended dose of ALIMTA, administered when administered with cisplatin, in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m^2 as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity.

2.3 Renal Impairment

- ALIMTA dosing recommendations are provided for patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater *[see Dosage and Administration (2.1, 2.2)]*. There is no recommended dose for patients whose creatinine clearance is less than 45 mL/min *[see Use in Specific Populations (8.6)]*.

2.4 Premedication and Concomitant Medications to Mitigate Toxicity

Vitamin Supplementation

- Initiate folic acid 400 mcg to 1000 mcg orally once daily, beginning 7 days before the first dose of ALIMTA and continuing until 21 days after the last dose of ALIMTA *[see Warnings and Precautions (5.1)]*.

- Administer vitamin $B_{12,}$ 1 mg intramuscularly, 1 week prior to the first dose of ALIMTA and every 3 cycles thereafter. Subsequent vitamin B_{12} injections may be given the same day as treatment with ALIMTA *[see Warnings and Precautions (5.1)]*. **Do not substitute oral vitamin B_{12} for intramuscular vitamin B_{12}.**

Corticosteroids

- Administer dexamethasone 4 mg orally twice daily for three consecutive days, beginning the day before each ALIMTA administration.

2.5 Dosage Modification of Ibuprofen in Patients with Mild to Moderate Renal Impairment Receiving ALIMTA

In patients with creatinine clearances between 45 mL/min and 79 mL/min, modify administration of ibuprofen as follows *[see Warnings and Precautions (5.6), Drug Interactions (7) and Clinical Pharmacology (12.3)]*:

- Avoid administration of ibuprofen for 2 days before, the day of, and 2 days following administration of ALIMTA.
- Monitor patients more frequently for myelosuppression, renal, and gastrointestinal toxicity, if concomitant administration of ibuprofen cannot be avoided.

2.6 Dosage Modifications for Adverse Reactions

Obtain complete blood count on Days 1, 8, and 15 of each cycle. Assess creatinine clearance prior to each cycle. Do not administer ALIMTA if the creatinine clearance is less than 45 mL/min.

Delay initiation of the next cycle of ALIMTA until:

- recovery of non-hematologic toxicity to Grade 0-2,
- absolute neutrophil count (ANC) is 1500 cells/mm^3 or higher, and
- platelet count is 100,000 cells/mm^3 or higher.

Upon recovery, modify the dosage of ALIMTA in the next cycle as specified in Table 1.

For dosing modifications for cisplatin, refer to the prescribing information for cisplatin.

Table 1: Recommended Dosage Modifications for Adverse Reactions[a]

Toxicity in Most Recent Treatment Cycle	ALIMTA Dose Modification for Next Cycle
Myelosuppressive toxicity *[see Warnings and Precautions (5.1)]*	
ANC less than 500/mm^3 **and** platelets greater than or equal to 50,000/mm^3 OR Platelet count less than 50,000/mm^3 without bleeding.	75% of previous dose
Platelet count less than 50,000/mm^3 with bleeding	50% of previous dose
Recurrent Grade 3 or 4 myelosuppression after 2 dose reductions	Discontinue
Non-hematologic toxicity	
Any Grade 3 or 4 toxicities EXCEPT mucositis or neurologic toxicity OR Diarrhea requiring hospitalization	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose
Renal toxicity *[see Warnings and Precautions (5.2)]*	Withhold until creatinine clearance is 45 mL/min or greater
Grade 3 or 4 neurologic toxicity	Permanently discontinue
Recurrent Grade 3 or 4 non-hematologic toxicity after 2 dose reductions	Permanently discontinue
Severe and life-threatening Skin Toxicity *[see Warnings and Precautions (5.3)]*	Permanently discontinue
Interstitial Pneumonitis *[see Warnings and Precautions (5.4)]*	Permanently discontinue

[a] National Cancer Institute Common Toxicity Criteria for Adverse Events version 2 (NCI CTCAE v2).

2.7 Preparation for Administration

- ALIMTA is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]
- Calculate the dose of ALIMTA and determine the number of vials needed.
- Reconstitute ALIMTA to achieve a concentration of 25 mg/mL as follows:
  - Reconstitute each 100-mg vial with 4.2 mL of 0.9% Sodium Chloride Injection, USP (preservative-free)
  - Reconstitute each 500-mg vial with 20 mL of 0.9% Sodium Chloride Injection, USP (preservative-free)
  - Do not use calcium-containing solutions for reconstitution.
- Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in color from colorless to yellow or green-yellow. FURTHER DILUTION IS REQUIRED prior to administration.
- Store reconstituted, preservative-free product under refrigerated conditions [2-8°C (36-46°F)] for no longer than 24 hours from the time of reconstitution. Discard vial after 24 hours.
- Inspect reconstituted product visually for particulate matter and discoloration prior to further dilution. If particulate matter is observed, discard vial.
- Withdraw the calculated dose of ALIMTA from the vial(s) and discard vial with any unused portion.
- Further dilute ALIMTA with 0.9% Sodium Chloride Injection (preservative-free) to achieve a total volume of 100 mL for intravenous infusion.
- Store diluted, reconstituted product under refrigerated conditions [2-8°C (36-46°F)] for no more than 24 hours from the time of reconstitution. Discard after 24 hours.

3 DOSAGE FORMS AND STRENGTHS

For injection: 100 mg or 500 mg pemetrexed as a white to light-yellow or green-yellow lyophilized powder in single-dose vials for reconstitution.

4 CONTRAINDICATIONS

ALIMTA is contraindicated in patients with a history of severe hypersensitivity reaction to pemetrexed *[see Adverse*

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression and Increased Risk of Myelosuppression without Vitamin Supplementation

ALIMTA can cause severe myelosuppression resulting in a requirement for transfusions and which may lead to neutropenic infection. The risk of myelosuppression is increased in patients who do not receive vitamin supplementation. In Study JMCH, incidences of Grade 3-4 neutropenia (38% versus 23%), thrombocytopenia (9% versus 5%), febrile neutropenia (9% versus 0.6%), and neutropenic infection (6% versus 0) were higher in patients who received ALIMTA plus cisplatin without vitamin supplementation as compared to patients who were fully supplemented with folic acid and vitamin B_{12} prior to and throughout ALIMTA plus cisplatin treatment.

Initiate supplementation with oral folic acid and intramuscular vitamin B_{12} prior to the first dose of ALIMTA; continue vitamin supplementation during treatment and for 21 days after the last dose of ALIMTA to reduce the severity of hematologic and gastrointestinal toxicity of ALIMTA *[see Dosage and Administration (2.4)]*. Obtain a complete blood count at the beginning of each cycle. Do not administer ALIMTA until the ANC is at least 1500 cells/mm^3 and platelet count is at least 100,000 cells/mm^3. Permanently reduce ALIMTA in patients with an ANC of less than 500 cells/mm^3 or platelet count of less than 50,000 cells/mm^3 in previous cycles *[see Dosage and Administration (2.6)]*.

In Studies JMDB and JMCH, among patients who received vitamin supplementation, incidence of Grade 3-4 neutropenia was 15% and 23%, the incidence of Grade 3-4 anemia was 6% and 4%, and incidence of Grade 3-4 thrombocytopenia was 4% and 5%, respectively. In Study JMCH, 18% of patients in the ALIMTA arm required red blood cell transfusions compared to 7% of patients in the cisplatin arm *[see Adverse Reactions (6.1)].* In Studies JMEN, PARAMOUNT, and JMEI, where all patients received vitamin supplementation, incidence of Grade 3-4 neutropenia ranged from 3% to 5%, and incidence of Grade 3-4 anemia ranged from 3% to 5%.

5.2 Renal Failure

ALIMTA can cause severe, and sometimes fatal, renal toxicity. The incidences of renal failure in clinical studies in which patients received ALIMTA with cisplatin were: 2.1% in Study JMDB and 2.2% in Study JMCH. The incidence of renal failure in clinical studies in which patients received ALIMTA as a single agent ranged from 0.4% to 0.6% (Studies JMEN, PARAMOUNT, and JMEI *[see Adverse Reactions (6.1)]*. Determine creatinine clearance before each dose and periodically monitor renal function during treatment with ALIMTA. Withhold ALIMTA in patients with a creatinine clearance of less than 45 mL/minute *[see Dosage and Administration (2.3)]*.

5.3 Bullous and Exfoliative Skin Toxicity

Serious and sometimes fatal, bullous, blistering and exfoliative skin toxicity, including cases suggestive of Stevens-Johnson Syndrome/Toxic epidermal necrolysis can occur with ALIMTA. Permanently discontinue ALIMTA for severe and life-threatening bullous, blistering or exfoliating skin toxicity.

5.4 Interstitial Pneumonitis

Serious interstitial pneumonitis, including fatal cases, can occur with ALIMTA treatment. Withhold ALIMTA for acute onset of new or progressive unexplained pulmonary symptoms such as dyspnea, cough, or fever pending diagnostic evaluation. If pneumonitis is confirmed, permanently discontinue ALIMTA.

5.5 Radiation Recall

Radiation recall can occur with ALIMTA in patients who have received radiation weeks to years previously. Monitor patients for inflammation or blistering in areas of previous radiation treatment. Permanently discontinue ALIMTA for signs of radiation recall.

5.6 Increased Risk of Toxicity with Ibuprofen in Patients with Renal Impairment

Exposure to ALIMTA is increased in patients with mild to moderate renal impairment who take concomitant ibuprofen, increasing the risks of adverse reactions of ALIMTA. In patients with creatinine clearances between 45 mL/min and 79 mL/min, avoid administration of ibuprofen for 2 days before, the day of, and 2 days following administration of ALIMTA. If concomitant ibuprofen use cannot be avoided, monitor patients more frequently for ALIMTA adverse reactions, including myelosuppression, renal, and gastrointestinal toxicity *[see Dosage and Administration (2.5), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

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