

**POLICY:** Oncology - Alimta<sup>®</sup> (pemetrexed for injection, for intravenous use) – Eli Lilly and Company)

**APPROVAL DATE:** 10/16/2019

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## OVERVIEW

Alimta is indicated for locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) as initial treatment in combination with cisplatin; as initial treatment in combination with platinum chemotherapy and Keytruda (pembrolizumab for injection) in patients with no EGFR or ALK genomic tumor aberrations; as maintenance treatment of patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy; or after prior chemotherapy as a single agent.<sup>1</sup> Alimta is not indicated for the treatment of patients with squamous cell NSCLC. Alimta in combination with cisplatin is also indicated for treatment of patients with malignant pleural mesothelioma (MPM) whose disease is unresectable or who are otherwise not candidates for curative surgery. Alimta is a folate analog metabolic inhibitor that disrupts folate-dependent metabolic processes essential for cell replication.<sup>1</sup>

Concomitant vitamin supplementation and premedication are required with Alimta therapy to reduce toxicity.<sup>1</sup> Supplementation with oral folic acid 400 mcg to 1,000 mcg once daily should begin 7 days before the first dose of Alimta and continued during the full course of therapy and for 21 days after the last dose of Alimta. Intramuscular vitamin B12 (cyanocobalamin) 1 mg is required one week prior to the first dose of Alimta and every 3 cycles thereafter; subsequent vitamin B12 injections may be given the same day as treatment with Alimta. Premedication is required with oral dexamethasone 4 mg twice daily the day before, the day of, and the day after Alimta is given to reduce the risk of severe skin rash.

Alimta is available as a lyophilized powder in single-use 100 mg and 500 mg vials.<sup>1</sup> The 100 mg vials are reconstituted with 4.2 mL of 0.9% sodium chloride (NaCl) injection and the 500 mg vials are reconstituted with 20 mL of 0.9% NaCl injection. The final solution will contain 25 mg of Alimta per mL. The appropriate amount of reconstituted Alimta is diluted with 0.9% NaCl so the total volume is 100 mL. Alimta is given as an intravenous infusion over 10 minutes.

## Clinical Efficacy and Dosing

In one Phase II study, patients (n = 11) with relapsed or refractory PCNSL received single-agent Alimta 900 mg/m<sup>2</sup> every 3 weeks until complete remission, progression, or toxicity.<sup>2</sup> One cycle was six weeks. The dose of Alimta was chosen to optimize CNS penetration. Ten of the patients had failed prior therapy with high-dose MTX. The median number of treatment cycles of Alimta given was five (range, 1 to 7). The ORR was 55% with four CRs and two PRs. Six-month progression-free survival (PFS) was 45%, median PFS was 5.7 months, and median overall survival was 10.1 months.

In one Phase II trial, previously treated patients with thymomas (n = 16) or thymic carcinomas (n = 11) received Alimta 500 mg/m<sup>2</sup> every 3 weeks for a maximum of 6 cycles.<sup>3</sup> In 23 patients who were fully evaluable there were two CRs and two PRs. All of these patients had thymomas. In one retrospective analysis, patients (n = 16) with unresectable, invasive, recurrent or metastatic thymoma (n = 6) or thymic (n = 10) carcinomas who had received Alimta 500 mg/m<sup>2</sup> every 3 weeks as second-line therapy and beyond were reviewed.<sup>4</sup> The median number of cycles was six. In the patients with thymoma, one patient had a PR and five patients had stable disease, and at a median follow-up of 21.2 months, the PFS was 13.8 months and median overall survival was 20.1 months. In patients with thymic carcinoma one patient had a PR, five patients had stable disease, and four patients had progressive disease, and at a median follow-up of 13.5 months, the median PFS was 6.5 months and the median overall survival was 12.7 months.

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In one Phase II multicenter trial, patients (n = 47) previously treated with one prior chemotherapy regimen for locally advanced or metastatic urothelial carcinoma or who had relapsed within 1 year of adjuvant or neoadjuvant therapy received single-agent Alimta 500 mg/m<sup>2</sup> every 3 weeks.<sup>5</sup> The ORR was 27.7% with 6.4% (n = 3/47) CRs and 21.3% (n = 10/47) PRs. Ten patients had stable disease. Median overall survival was 9.6 months (95% CI: 5.1, 14.6). Median duration of response was 5.0 months. In one Phase II study conducted in Korea, patients (n = 42) with recurrent or metastatic urothelial carcinoma received Alimta 500 mg/m<sup>2</sup> with cisplatin every 3 weeks.<sup>6</sup> Seven patients had received platinum-based adjuvant or neoadjuvant chemotherapy. No patients had a CR and 64.3% of patients (n = 27/42) had a PR. Median PFS was 6.9 months and median overall survival was 14.4 months. The median number of cycles given was eight (range, 1 to 8).

### Guidelines

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines on NSCLC (version 7.2019 – August 30, 2019) recommend Alimta for patients with adenocarcinoma (with mixed subtypes) or large cell carcinoma (i.e., non-squamous cell NSCLC) in a wide variety of treatment settings.<sup>7</sup> Some of the places in therapy for Alimta include as concurrent chemoradiation in combination with cisplatin or carboplatin either in preoperative or adjuvant setting; and as part of chemotherapy regimen in the adjuvant and neoadjuvant setting. Alimta is also used in combination therapy with cisplatin or carboplatin ± Avastin and in combination with Keytruda + cisplatin/carboplatin as initial cytotoxic therapy options in adenocarcinoma, large-cell, NSCLC not-otherwise-specified (NOS) for performance status (PS) 0 to 1. Alimta is also used as part of a combination regimen as a subsequent therapy option in patients who have progressed on targeted therapies for targetable mutations (e.g., sensitizing *EGFR* mutation-positive tumors, *ALK* rearrangement-positive tumors, *ROS1* rearrangement-positive tumors). It can also be used as first-line or subsequent therapy for *BRAF V600E* or neurotrophic tyrosine receptor kinase (*NTRK*) gene-fusion positive NSCLC. Alimta can also be used as continuation maintenance therapy either alone or in combination with Keytruda or as monotherapy for switch maintenance. Alimta is not recommended in patients with squamous cell NSCLC.

The NCCN clinical practice guidelines on MPM (version 2.2019 – April 1, 2019) recommend Alimta for MPM (histologies epithelial, sarcomatoid, or mixed) for the following uses:<sup>8,9</sup>

- induction therapy in combination with cisplatin/carboplatin (category 2A);
- single agent or in combination with cisplatin or carboplatin for the treatment of unresectable disease .
- in combination with Avastin and cisplatin/carboplatin for treatment of unresectable disease and tumors of epithelial histology or for clinical Stage IV disease, tumors of sarcomatoid or mixed histology, or medically inoperable tumors in patients with PS 0 to 2 (category 1); and
- subsequent treatment as a single agent in patients with a good sustained response at the time initial chemotherapy was interrupted (category 1).

These guidelines also state that Alimta-based chemotherapy may also be used for peritoneal mesothelioma, pericardial mesothelioma, and tunica vaginalis testis mesothelioma.<sup>4</sup>

The NCCN clinical practice guidelines on ovarian cancer including fallopian tube cancer and primary peritoneal cancer (version 2.2019 – September 17, 2019) recommends Alimta as single agent therapy for persistent disease or recurrence in platinum-sensitive or platinum-recurrent setting (category 2A).<sup>10</sup>

The NCCN clinical practice guidelines on CNS cancers (version 2.2019 – September 16, 2019) recommend Alimta as one of the treatments for relapsed or refractory disease in patients with PCNSL.<sup>11</sup>

The NCCN clinical practice guidelines on thymomas and thymic carcinomas (version 2.2019 – March 11, 2019) recommends single agent Alimta as a second-line chemotherapy for thymic carcinoma or thymoma (category 2A).<sup>12</sup> First-line combination chemotherapy regimens include cisplatin- or carboplatin-based therapy.

The NCCN clinical practice guidelines on bladder cancer (version 4.20189 – July 10, 2019) recommend Alimta as a single agent for urothelial carcinoma for locally advanced or metastatic disease, post-platinum or post-checkpoint inhibitor therapy (category 2A).<sup>13</sup>

### **POLICY STATEMENT**

This policy involves the use of Alimta infusion. Prior authorization is recommended for medical benefit coverage of Alimta. Approval is recommended for those who meet the conditions of coverage for Criteria and Dosing. Because of the of the specialized skills required for evaluation and diagnosis of patients treated with Alimta as well as the monitoring required for adverse events and long-term efficacy, approval requires Alimta to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

### **RECOMMENDED AUTHORIZATION CRITERIA**

Coverage of Alimta is recommended in those who meet one of the following criteria:

#### **FDA-Approved Indications**

- I. Non-Small Cell Lung Cancer (NSCLC):** Approve for 1 year if the patient meets the following criteria (A, B, and C):
  - A)** Alimta is prescribed by or in consultation with an oncologist; **AND**
  - B)** The patient has non-squamous cell non-small cell lung cancer (NSCLC);<sup>1-2</sup> **AND**
  - C)** The patient meets **ONE** of the following criteria (i or ii):
    - i.** Alimta is used for chemoradiation, perioperative, neoadjuvant, or adjuvant therapy in combination with platinum chemotherapy (e.g., cisplatin, carboplatin); **OR**
    - ii.** Alimta is used for recurrent or metastatic disease and the following conditions are met (a, b, or c):
      - a)** If the NSCLC tumor is positive for any of the targetable mutations (e.g., epidermal growth factor receptor [*EGFR*] mutation, anaplastic lymphoma kinase [*ALK*] fusions, ROS proto-oncogene 1 [*ROS1*]), at least one of the targeted therapy has been tried and Alimta is used as subsequent therapy; **OR**
      - b)** If the NSCLC tumor is *BRAF V600E* mutation-positive or neurotrophic tyrosine receptor kinase (NTRK) gene fusion-positive, Alimta is used as either first-line therapy or subsequent therapy; **OR**
      - c)** The NSCLC tumor is negative or unknown for targetable mutations (e.g., *EGFR*, *ALK*, *ROS1*, *BRAF*) and the patient meets **ONE** of the following criteria (1 or 2):
        - (1)** Alimta is used as initial therapy in combination with platinum chemotherapy (cisplatin or carboplatin) either with or without Keytruda® (pembrolizumab intravenous injection); **OR**
        - (2)** Alimta is used as subsequent therapy and is used either as a single agent or in combination with other agents.

**Dosing.** Approve up to 500 mg per m<sup>2</sup> intravenous infusion not more frequently than once every 3 weeks.

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- 2. Mesothelioma:** Approve for 1 year if the patient meets the following criteria (A and B):
- A) Alimta is prescribed by or in consultation with an oncologist; AND
  - B) The patient meets ONE of the following criteria (i or ii):
    - i. Alimta is used for malignant pleural mesothelioma (MPM);<sup>1,4</sup> OR
    - ii. Alimta is used for malignant peritoneal mesothelioma, pericardial mesothelioma, or tunica vaginalis testis mesothelioma.<sup>4</sup>

**Dosing.** Approve up to 500 mg per m<sup>2</sup> as an intravenous infusion not more frequently than once every 3 weeks.<sup>1</sup>

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**Other Uses with Supportive Evidence**

- 3. Ovarian, Fallopian Tube, or Primary Peritoneal Cancer:** Approve for 1 year if the patient meets the following criteria (A, B, and C):
- A) Alimta is prescribed by or in consultation with an oncologist; AND
  - B) The patient has persistent or recurrent disease; AND
  - C) At least one other systemic chemotherapy regimen has been tried.
- Note: Examples of chemotherapy are docetaxel, paclitaxel, gemcitabine, cisplatin, carboplatin, .

**Dosing.** Approve up to 500 mg per m<sup>2</sup> as an intravenous infusion not more frequently than once every 3 weeks.<sup>16</sup>

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- 4. Primary Central Nervous System (CNS) Lymphoma [PCNSL]:** Approve for 1 year if the patient meets the following criteria (A, B, and C):
- A) Alimta is prescribed by or in consultation with an oncologist; AND
  - B) The patient has relapsed or refractory disease; AND
  - C) The patient has received at least one prior therapy (e.g., methotrexate-based regimen, high-dose chemotherapy plus stem cell rescue).

**Dosing.** Approve up to 900 mg per m<sup>2</sup> as an intravenous infusion not more frequently than once every 3 weeks.<sup>19</sup>

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- 5. Thymic Carcinoma or Thymoma:** Approve for 1 year if the patient meets the following criteria (A and B):
- A) Alimta is prescribed by or in consultation with an oncologist; AND
  - B) The patient has tried at least one prior chemotherapy regimen. ,
- Note: Examples of chemotherapy are cisplatin plus doxorubicin, cisplatin plus etoposide, carboplatin plus paclitaxel.

**Dosing.** Approve up to 500 mg per m<sup>2</sup> as an intravenous infusion not more frequently than once every 3 weeks.<sup>21-22</sup>

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- 6. Urothelial Carcinoma:** Approve for 1 year if the patient meets the following criteria (A, B, and C):
- A) Alimta is prescribed by or in consultation with an oncologist; AND
  - B) The patient has locally advanced or metastatic urothelial carcinoma; AND
  - C) Alimta is used as subsequent therapy after disease progression on at least one prior therapy.

Note: Examples of chemotherapy are cisplatin- or carboplatin-containing regimen, immunotherapy [Keytruda<sup>®</sup> {pembrolizumab injection}, Tecentriq<sup>®</sup> {atezolizumab injection}, Imfinzi<sup>™</sup> {durvalumab injection}, Bavencio<sup>®</sup> {avelumab injection}], gemcitabine plus paclitaxel, ifosfamide, methotrexate, Abraxane<sup>®</sup> [paclitaxel albumin-bound].

**Dosing.** Approve up to 500 mg per m<sup>2</sup> as an intravenous infusion not more frequently than once every 3 weeks.<sup>24-25</sup>

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### CONDITIONS NOT RECOMMENDED FOR APPROVAL

Alimta has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval). Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

### REFERENCES

1. Alimta<sup>®</sup> for injection [prescribing information]. Indianapolis, IN: Eli Lilly and Company; February 2015.
2. Raizer JJ, Rademaker A, Evens AM, et al. Pemetrexed in the treatment of relapsed/refractory primary central nervous system lymphoma. *Cancer*. 2012;118:3743-3748.
3. Loehrer PJ, Yiannoutsos CT, Dropcho S, et al. A phase II trial of pemetrexed in patients with recurrent thymoma or thymic carcinoma [abstract]. *J Clin Oncol*. 2006;24(June 20 Supplement):7079.
4. Liang Y, Padda SK, Riess JW, et al. Pemetrexed in patients with thymic malignancies previously treated with chemotherapy. *Lung Cancer*. 2015;87:34-38.
5. Sweeney CJ, Roth BJ, Kabbinar FF, et al. Phase II study of pemetrexed for second-line treatment of transitional cell cancer of the urothelium. *J Clin Oncol*. 2006;24:3451-3457.
6. Choi YJ, Lee SH, Lee JL, et al. Phase II study of pemetrexed in combination with cisplatin in patients with advanced urothelial cancer: the PECULIAR study (KCSG 10-17). *Br J Cancer*. 2015;112:260-265.
7. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 7.2019 – August 30, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on October 14, 2019.
8. The NCCN Drugs & Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on October 9, 2019. Search term: pemetrexed.
9. The NCCN Malignant Pleural Mesothelioma Clinical Practice Guidelines in Oncology (Version 2.2019 – April 1, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on October 14, 2019.
10. The NCCN Ovarian Cancer Clinical Practice Guidelines in Oncology (Version 2.2019 – September 17, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on October 14, 2019.
11. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (Version 2.2019 – September 16, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on October 14, 2019.
12. The NCCN Thymomas and Thymic Carcinomas Clinical Practice Guidelines in Oncology (Version 2.2019 – March 11, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on October 14, 2019.
13. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (Version 4.2019 – July 10, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on October 14, 2019.

**HISTORY**

Type of Revision	Summary of Changes	Approval Date
Annual	<p>In patients with recurrent or metastatic NSCLC, criteria were revised to add that testing has been completed for <i>EGFR</i> exon 19 deletion or exon 21 (L858R) substitution, <i>ALK</i> fusions, and <i>ROS1</i> rearrangements and prior targeted therapy is required if appropriate. Also added use for chemoradiation, perioperative, neoadjuvant, or adjuvant therapy (where prior testing in not required). Criteria were added for ovarian, fallopian tube, or primary peritoneal cancer; primary CNS lymphoma, thymic carcinoma or thymoma; and urothelial carcinoma.</p>	07/27/2016
Annual	<p>For NSCLC the list of targeted therapies used for each aberration was removed; <i>EGFR</i>, <i>ALK</i>, and <i>ROS1</i> are negative was added as an option after testing; criterion requiring testing for PD-L1 was added and requirement to try Keytruda therapy for patients with PD-L1 expression <math>\geq 50\%</math> was added. Number of cycles allowed for chemoradiation, perioperative, neoadjuvant, or adjuvant therapy was increased to seven. Urothelial carcinoma criteria were revised to add that in addition to having tried chemotherapy, immunotherapy with Keytruda or Tecentriq would be an option. The exception for a platinum-containing chemotherapy regimen or other chemotherapy is contraindicated was removed. Keytruda or Tecentriq could be used in this circumstance.</p>	08/23/2017
Annual revision	<ul style="list-style-type: none"> <li>• For all indications approval (initial/extended) was changed to 1 year. Lab/Diagnositics was changed to “none required”.</li> <li>• Criteria for “Patient has been started on Alimta” has been deleted, in line with other MBM policies</li> <li>• For Duration of therapy, verbiage has been changed to determined by prescriber and patient must meet criteria for approval and dosing.</li> <li>• <b>Non-Small Cell Lung Cancer:</b> For use in chemoradiation, perioperative, neoadjuvant/adjuvant therapy, criteria was added that Alimta is used “in combination with platinum chemotherapy (cisplatin or carboplatin).             <ul style="list-style-type: none"> <li>• Deleted all criteria requiring testing for targetable mutations and for programmed death ligand 1 expression.</li> <li>• Added criteria for metastatic disease that if NSCLC tumor is positive for targetable mutation, the patient has tried at least one targeted therapy and Alimta will be used as subsequent therapy.</li> <li>• Added new criteria for BRAF V600E mutation that Alimta can be used either as first-line or subsequent therapy. Under Labs/Diagnostics, added Note that BRAF V600E mutation may be checked as part of above new criteria. Also, added criteria that if NSCLC tumor is negative or unknown for targetable mutation, that Alimta is used as initial therapy in combination with platinum chemo with or without Keytruda; OR that Alimta is used as subsequent therapy and is used either as single agent or in combination.</li> </ul> </li> <li>• <b>Mesothelioma:</b> Added “pericardial mesothelioma” in criteria Bii.</li> <li>• <b>Primary Central Nervous System Lymphoma (PCNSL):</b> Reworded criteria (B) to “relapsed or refractory disease” and deleted “recurrent or progressive PCNSL” based on NCCN guidelines.             <ul style="list-style-type: none"> <li>• Also added new criteria that “Patient has received at least one prior therapy (e.g., methotrexate-based regimen, high-dose chemotherapy plus stem cell rescue)”.</li> </ul> </li> <li>• <b>Thymic carcinoma or Thymoma:</b> In criteria (B) added “at least one prior” chemotherapy regimen and listed examples as before in parentheses.</li> <li>• <b>Urothelial Carcinoma:</b> Deleted “recurrent” when referring to locally advanced or metastatic disease.             <ul style="list-style-type: none"> <li>• Re-worded previous criteria (C) to state that “Alimta is used as subsequent therapy after disease progression on at least one prior therapy” and provided examples of prior therapies in parantheses.</li> </ul> </li> </ul>	10/03/2018

Type of Revision	Summary of Changes	Approval Date
Annual revision	<ul style="list-style-type: none"><li>• <b>Non-Small Cell Lung Cancer:</b> For use of Alimta as initial or subsequent therapy, added “and neurotrophic tyrosine receptor kinase (NTRK)” in criteria referring to BRAF mutations.</li><li>• <b>Dosing:</b> For all indications in the Dosing, added “Approve up to” and also added “not more frequently than once every 3 weeks.”</li><li>• <b>Other Cancer-Related Indications:</b> Deleted approval condition in-line with other policies.</li><li>• Deleted Waste Management, Initial/Extended Approval, Duration of Therapy, and Labs/Diagnostics sections from policy.</li></ul>	10/16/2019