

UTILIZATION MANAGEMENT MEDICAL POLICY

- POLICY:** Oncology (Injectable) – Pemetrexed Products Utilization Management Medical Policy
- Alimta® (pemetrexed intravenous infusion – Eli Lilly, generics)
 - Pemfexy™ (pemetrexed intravenous infusion – Eagle)
 - Pemrydi RTU™ (pemetrexed disodium intravenous infusion – Amneal/Zydus)

REVIEW DATE: 01/22/2025

OVERVIEW

Pemetrexed (Alimta, Pemfexy, Pemrydi RTU, generic) is indicated for the following conditions:^{1,2}

- **Malignant pleural mesothelioma**, initial treatment of unresectable disease or in patients who are otherwise not candidates for curative surgery, in combination with cisplatin.
- **Non-small cell lung cancer (NSCLC)**, locally advanced or metastatic non-squamous disease, as initial treatment in combination with cisplatin.
- **NSCLC**, as initial treatment in combination with platinum chemotherapy and Keytruda® (pembrolizumab intravenous infusion) in patients with metastatic non-squamous disease with no epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations (only Alimta).
- **NSCLC**, as a single agent, for the maintenance treatment of patients with locally advanced or metastatic non-squamous disease who have not progressed after four cycles of platinum-based first-line chemotherapy.
- **NSCLC**, as a single agent for the treatment of patients with recurrent, metastatic, non-squamous disease after prior chemotherapy.

Limitations of Use: Alimta, Pemfexy, and Pemrydi RTU are not indicated for the treatment of patients with squamous cell NSCLC.

Guidelines

The National Comprehensive Cancer Network guidelines address the use of pemetrexed:

- **Cervical Cancer:** NCCN guidelines (version 1.2025 – December 19, 2024) recommend pemetrexed for the second-line or subsequent treatment of recurrent or metastatic disease.^{4,13}
- **Mesothelioma:** The malignant pleural mesothelioma guidelines (version 2.2025 – January 14, 2025) and the malignant peritoneal mesothelioma guidelines (version 2.2025 – January 14, 2025) recommend pemetrexed for induction or first-line therapy in combination with cisplatin or carboplatin, with or without Keytruda (pembrolizumab intravenous infusion) or bevacizumab; or as a single agent.^{4,5,12} Pemetrexed is also recommended for subsequent treatment as a single agent, or in combination with cisplatin or carboplatin, with or without bevacizumab. These guidelines also state that pemetrexed-based chemotherapy may also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma.
- **Non-Small Cell Lung Cancer:** Guidelines (version 3.2025 – January 14, 2025) recommend pemetrexed for non-squamous cell NSCLC in a wide variety of treatment settings.^{3,4} Some of the places in therapy for pemetrexed include as concurrent chemoradiation in combination with cisplatin or carboplatin either in the preoperative or adjuvant setting; and as part of chemotherapy regimen in the adjuvant and neoadjuvant setting. Pemetrexed is also used in combination therapy with cisplatin or carboplatin ± bevacizumab; in combination with Keytruda + cisplatin/carboplatin; and in combination with Opdivo® (nivolumab intravenous infusion) + Yervoy® (ipilimumab intravenous infusion) as initial cytotoxic therapy options for performance status 0 to 2. Pemetrexed

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, *MET* exon 14 skipping mutation, and *RET* rearrangement positive NSCLC. Pemetrexed can also be used as continuation maintenance therapy either alone or in combination with Keytruda or as monotherapy for switch maintenance. Pemetrexed is not recommended in patients with squamous cell NSCLC.

- **Ovarian, Fallopian Tube, and Primary Peritoneal Cancer:** Guidelines (version 3.2024 – July 15, 2024) recommend pemetrexed as single agent for persistent disease or recurrence in platinum-sensitive or platinum-recurrent setting (category 2A).^{4,6}
- **Primary Central Nervous System Lymphoma:** Guidelines (version 3.2024 – September 30, 2024) recommend pemetrexed as a single agent for induction therapy if the patient is unsuitable or intolerant of high-dose methotrexate and as treatment for relapsed or refractory disease.^{4,7}
- **Thymomas and Thymic Carcinoma:** Guidelines (version 1.2025 – October 30, 2024) recommend single agent pemetrexed for patients who cannot tolerate first-line combination regimens and as a second-line chemotherapy for thymic carcinoma or thymoma (category 2A).^{4,8}
- **Vaginal Cancer:** Guidelines (version 3.2025 – December 16, 2024) recommend pemetrexed as a single agent for the second-line and subsequent treatment of locoregional recurrence or metastatic disease.^{4,17}

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of pemetrexed. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with pemetrexed as well as the monitoring required for adverse events and long-term efficacy, approval requires the medication to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

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1. **Mesothelioma.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
 - A) Patient is ≥ 18 years of age; AND
 - B) Patient meets ONE of the following criteria (i or ii):
 - i. The medication is used for malignant pleural mesothelioma; OR
 - ii. The medication is used for malignant peritoneal mesothelioma, pericardial mesothelioma, or tunica vaginalis testis mesothelioma; AND
 - C) The medication is prescribed by or in consultation with an oncologist.
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Dosing. Approve up to 500 mg/m² as an intravenous infusion administered not more frequently than once every 3 weeks.

2. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient has non-squamous cell non-small cell lung cancer (NSCLC); AND

Note: This includes adenocarcinoma, large cell, NSCLC not otherwise specified.

C) Patient meets ONE of the following criteria (i or ii):

i. The medication is used for chemoradiation, perioperative, neoadjuvant, adjuvant, or induction therapy in combination with platinum chemotherapy; OR

Note: Examples of platinum chemotherapy include cisplatin and carboplatin.

ii. The medication is used for recurrent, advanced, or metastatic disease and ONE of the following conditions are met (a, b, c, d, e, or f):

a) The NSCLC tumor is negative or unknown for targetable mutations and the patient meets ONE of the following criteria [(1) or (2)]:

Note: Examples of targetable mutations include epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, ROS proto-oncogene 1 (*ROS1*) rearrangement-positive, *BRAF V600E* mutation-positive, *MET* exon 14 skipping mutation-positive, *RET* rearrangement positive, *NRG1*, or neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion-positive. May be *KRAS G12C* mutation positive.

(1) The medication is used as initial therapy in combination with one or more agents; OR
Note: Examples of other agents include platinum chemotherapy (cisplatin or carboplatin), Yervoy (ipilimumab intravenous infusion), PD-1 inhibitors (i.e., Opdivo [nivolumab intravenous infusion], Keytruda [pembrolizumab intravenous infusion]).

(2) The medication is used as maintenance or subsequent therapy and is used either as a single agent or in combination with other agents.

b) The medication is used as first-line therapy and the tumor is positive for ONE of the following [(1), (2), (3), (4), or (5)]:

(1) *EGFR* exon 20 insertion mutation; OR

(2) *EGFR* exon 19 deletion; OR

(3) Exon 21 *L858R* mutations; OR

(4) *NRG1* gene fusion; OR

(5) *ERBB2 (HER2)* mutation positive; OR

c) The medication is used as first-line or subsequent therapy and the tumor is positive for ONE of the following [(1), (2), (3), or (4)]:

(1) *BRAF V600E* mutation; OR

(2) *MET* exon 14 skipping mutation; OR

(3) *RET* rearrangement; OR

(4) Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion-positive; OR

d) The medication is used as subsequent therapy and the patient meets BOTH of the following [(1) and (2)]:

(1) The tumor is *EGFR* exon 19 deletion or exon 21 *L858R* mutation positive, *EGFR S768I*, *L861Q*, and/or *G719X* mutation positive, *ALK* rearrangement positive, *RET* rearrangement positive, or *ROS1* rearrangement positive; AND

(2) The patient has received targeted therapy for the specific mutation; OR

Note: Examples of targeted drug therapy include Gilotrif (afatinib tablets), Tagrisso (osimertinib tablets), erlotinib, Iressa (gefitinib tablets), Xalkori (crizotinib capsules),

Zykadia (ceritinib capsules), Alecensa (alectinib capsules), Alunbrig (brigatinib tablets), Lorbrena (lorlatinib tablets), Rozlytrek (entrectinib capsules), or Vizimpro (dacomitinib tablets).

- e) The medication is used as subsequent therapy if the medication has not been previously given; OR
 - f) The medication is used for intrathecal therapy and the patient meets BOTH of the following [(1) and (2)]:
 - (1) The patient has leptomeningeal metastases; AND
 - (2) The NSCLC is *EGFR* mutation positive; AND
- D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):

- A) Approve up to 500 mg/m² intravenous infusion administered not more frequently than once every 3 weeks; OR
- B) Leptomeningeal metastases: Approve up to 50 mg administered intrathecally on the following schedule (i and ii):
 - i. No more frequently than twice in the first week of therapy; AND
 - ii. Then no more frequently than once every 3 weeks.

Other Uses with Supportive Evidence

3. **Cervical Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

- A) Patient is ≥ 18 years of age; AND
- B) Patient has recurrent or metastatic disease; AND
- C) Medication is used as subsequent therapy; AND
- D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 900 mg/m² as an intravenous infusion administered not more frequently than once every 3 weeks.

4. **Ovarian, Fallopian Tube, or Primary Peritoneal Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):

- A) Patient is ≥ 18 years of age; AND
- B) At least one other systemic chemotherapy regimen has been tried; AND
Note: Examples of chemotherapy are docetaxel, paclitaxel, gemcitabine, cisplatin, carboplatin.
- C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 900 mg/m² as an intravenous infusion administered not more frequently than once every 3 weeks.

5. **Primary Central Nervous System Lymphoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):

- A) Patient is ≥ 18 years of age; AND
 - B) The medication is prescribed by or in consultation with an oncologist.
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Dosing. Approve up to 900 mg/m² as an intravenous infusion administered not more frequently than once every 3 weeks.

6. Thymic Carcinoma or Thymoma. Approve for 1 year if the patient meets BOTH of the following (A and B):

- A) Patient is ≥ 18 years of age; AND
- B) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 500 mg/m² as an intravenous infusion administered not more frequently than once every 3 weeks.

7. Vaginal Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

- A) Patient is ≥ 18 years of age; AND
- B) Patient has locoregional recurrence or metastatic disease; AND
- C) Medication is used as subsequent therapy; AND
- D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 500 mg/m² as an intravenous infusion administered not more frequently than once every 3 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of pemetrexed is not recommended in the following situations:

- 1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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- 3. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2025 – January 14, 2025). © 2025 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on January 16, 2025.
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15. Fan C, Zhao Q, Li L, et al. Efficacy and safety of intrathecal pemetrexed combined with dexamethasone for treating tyrosine kinase inhibitor-failed leptomeningeal metastases from EGFR-mutant NSCLC – a prospective, open-label, single-arm phase 1/2 clinical trial (unique identifier: ChiCTR1800016615). *J Thorac Oncol*. 2021;16:1359-1368.
16. Pemrydi RTU intravenous infusion [prescribing information]. Bridgewater, NJ: Amneal and Ahmedabad, India: Zydus Lifesciences; November 2024.
17. The NCCN Vaginal Cancer Clinical Practice Guidelines in Oncology (version 3.2025 – December 16, 2024). © 2024 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on January 14, 2025.

HISTORY

| Type of Revision | Summary of Changes | Review Date |
|-------------------|---|-------------|
| Annual Revision | <p>Non-Small Cell Lung Cancer: Added descriptor exon 21 to the requirement that the tumor is epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R mutation positive, EGFR S768I, L861Q, and/or G719X mutation positive, ALK rearrangement positive, or ROS1 rearrangement-positive. Added option for approval for intrathecal therapy for leptomeningeal metastases. Added intrathecal dosing to Dosing section.</p> <p>Cervical Cancer: Added new condition of approval.</p> | 12/20/2023 |
| Selected Revision | Pemrydi RTU: Pemrydi RTU added to the policy. | 06/19/2024 |
| Annual Revision | <p>Non-Small Cell Lung Cancer: Removed <i>KRAS</i> and added <i>NRG1</i> to list of targetable mutations in Note. Added May be <i>KRAS G12C</i> mutation positive to Note. Added descriptor “insertion” to <i>EGFR</i> exon 20 insertion mutation. Added <i>EGFR</i> exon 19 deletion, Exon 21 <i>L858R</i> mutations, and <i>NRG1</i> gene fusion; and removed <i>KRAS G12C</i> as options for approval for first-line use of pemetrexed. Added <i>RET</i> rearrangement positive to the requirement that the tumor is <i>EGFR</i> exon 19 deletion or exon 21 <i>L858R</i> mutation positive, <i>EGFR S768I</i>, <i>L861Q</i>, and/or <i>G719X</i> mutation positive, <i>ALK</i> rearrangement positive, <i>RET</i> rearrangement positive, or <i>ROS1</i> rearrange positive. Added the medication is used as subsequent therapy if the medication has not been previously given as new option for approval.</p> <p>Vaginal Cancer: Added new condition of approval.</p> | 01/22/2025 |