

Policy Name	Policy Number	Scope
Pemetrexed (Alimta®, Pefexy®)	MP-RX-FP-05-23	<input checked="" type="checkbox"/> MMM MA <input checked="" type="checkbox"/> MMM Multihealth

Service Category

- | | |
|--|---|
| <input type="checkbox"/> Anesthesia | <input type="checkbox"/> Medicine Services and Procedures |
| <input type="checkbox"/> Surgery | <input type="checkbox"/> Evaluation and Management Services |
| <input type="checkbox"/> Radiology Procedures | <input type="checkbox"/> DME/Prosthetics or Supplies |
| <input type="checkbox"/> Pathology and Laboratory Procedures | <input checked="" type="checkbox"/> Part B Drugs |

Service Description

This document addresses the use of Pemetrexed agents, including Alimta® (pemetrexed disodium) and Pefexy (pemetrexed). Pemetrexed is a folate analog metabolic inhibitor approved by the Food and Drug Administration (FDA) for the treatment of patients with malignant pleural mesothelioma whose disease is either unresectable or who are otherwise not candidates for curative surgery.

Background Information

Pemetrexed is a folate analog with a pyrimidine base structure, and it exerts its anti-tumor effects by suppressing both DNA synthesis and folate metabolism through inhibition of multiple target enzymes. What sets pemetrexed apart is its ability to inhibit several enzymes simultaneously, a feature that distinguishes it from other drugs like methotrexate, which primarily targets dihydrofolate reductase, and 5-fluorouracil and raltitrexed, which mainly focus on thymidine synthetase.

This multifaceted enzyme inhibition characteristic makes pemetrexed a potentially valuable option for treating cancers that have developed resistance to 5-fluorouracil, methotrexate, or raltitrexed. Pemetrexed functions as a "multitargeted" antifolate compound by disrupting two crucial pathways within folate metabolism: purine synthesis through inhibition of thymidylate synthase (TS) and dihydrofolate reductase (DHFR), as well as pyrimidine synthesis through the inhibition of glucinamide ribonucleotide formyl transferase (GARFT) and aminoimidazole carboxamide formyl transferase (AiCARFT), all of which are key enzymes in the folate metabolic pathway.

The FDA approved indications for Alimta and Pefexy include non-squamous (NSCLC) and malignant pleural mesothelioma.

Non-Small Lung Cancer

- In combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations (Alimta only*).
- In combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, (NSCLC).

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- 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.

Malignant Pleural Mesothelioma

- In 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.

The FDA states neither Alimta nor Pefexy are indicated for the treatment of patients with squamous cell, non-small cell lung cancer.

The National Comprehensive Cancer Network (NCCN) provides additional recommendations with a category 2A level of evidence for the use of pemetrexed in ovarian cancer, and thymomas and thymic carcinomas, and additional uses in NSCLC.

The NCCN panel includes category 1 recommendations for nonsquamous NSCLC continuation maintenance therapy for use of pembrolizumab in combination with pemetrexed if given first-line as part of pembrolizumab/carboplatin/pemetrexed or pembrolizumab/cisplatin/pemetrexed regimen. The NCCN panel also gives a category 1 and 2A recommendation for use of pemetrexed in combination with platinum-based therapy as adjuvant or neoadjuvant therapy in NSCLC (Kenmotsu 2020, Kreuter 2013, Zhang 2014).

The NCCN panel also gives a category 1 recommendation for use of pemetrexed in malignant mesothelioma as single agent, subsequent therapy.

The NCCN panel recommends that individuals with NSCLC be tested for actionable molecular markers, such as EGFR, ALK, ROS1, BRAF, NTRK, MET and RET mutations, before initiating first line therapy to help guide treatment. If there is insufficient tissue to allow testing for all of these markers, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.

*The NCCN panel does not differentiate between Alimta and Pefexy for any indication, including the use in NSCLC in combination with pembrolizumab and platinum therapy for initial treatment.

Definitions and Measures

- Chemotherapy: Medical treatment of a disease, particularly cancer, with drugs or other chemicals.
- ECOG or Eastern Cooperative Oncology Group Performance Status: A scale and criteria used by doctors and researchers to assess how an individual’s disease is progressing, assess how the disease affects the daily living

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abilities of the individual, and determine appropriate treatment and prognosis. This scale may also be referred to as the WHO (World Health Organization) or Zubrod score which is based on the following scale:

- 0 = Fully active, able to carry on all pre-disease performance without restriction
 - 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
 - 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
 - 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
 - 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
 - 5 = Dead
- Immune checkpoint inhibitor: A type of drug that blocks certain proteins made by some types of immune system cells, such as T cells, and some cancer cells. When these proteins are blocked, the “brakes” on the immune system are released and T cells are able to kill cancer cells better. Examples of checkpoint proteins found on T cells or cancer cells include programmed death (PD)-1, PD-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen (CTLA)-4/B7-1/B7-2.
 - Line of Therapy:
 - First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
 - Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
 - Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second-line therapy) are not effective or there is disease progression.
 - Maintenance therapy: Designed to maintain a condition to prevent a relapse.
 - Metastasis: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.
 - Non-small cell lung cancer: A group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of non-small cell lung cancer are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma.
 - Programmed death (PD)-1 proteins: PD-1 proteins are found on T-cells and attach to PD ligands (PD-L1) found on normal (and cancer) cells (see immune checkpoint inhibitor above). Normally, this process keeps T-cells from attacking other cells in the body. However, this can also prevent T-cells from attacking cancer cells in the body. Examples of FDA approved anti-PD-1 agents include Keytruda (pembrolizumab), Opdivo (nivolumab), and Libtayo (cemiplimab).
 - Programmed death ligand (PD-L)-1: The ligands found on normal (and cancer) cells to which the PD-1 proteins attach (see immune checkpoint inhibitor above). Cancer cells can have large amounts of PD-L1 on their surface, which helps them to avoid immune attacks. Examples of FDA approved anti-PD-L1 agents include Bavencio (avelumab), Tecentriq (atezolizumab), and Imfinzi (durvalumab).
 - Refractory Disease: Illness or disease that does not respond to treatment.

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Approved Indications

Pemetrexed agents (Alimta and Pemetrex) are approved by the FDA for the following indications:

- In combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations.
- In combination with cisplatin for the initial treatment of patients with locally advanced or metastatic non-squamous, non-small cell lung cancer (NSCLC).
- 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. It's important to note that pemetrexed is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer.
- 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.

Other Uses

The NCCN also provides a category 2A recommendation for use in thymic cancer and thymomas as first-line therapy when preferred first-line combination regimens are not tolerated. At this time, there is insufficient data to support such use.

The NCCN CPGs in Oncology for primary CNS lymphoma include a recommendation for the use of pemetrexed in the treatment of recurrent or progressive primary CNS lymphoma. The 2A recommendation is based on a single study conducted by Raizer and colleagues (2012) which enrolled 11 participants with relapsed/refractory PCNSL to assess for single agent activity based on OS, PFS and response rates. Ten of the 11 participants had previously been treated with high-dose methotrexate. The 6-month PFS was 45%, median PFS was 5.7 months and median OS was 10.1 months. Toxicities experienced were largely infectious and hematologic. Authors conclude that pemetrexed demonstrated single-agent activity in relapsed/refractory PCNSL. At this time, the published data does not demonstrate the efficacy of pemetrexed in the treatment of PCNSL.

NCCN CPG for mesothelioma also includes a 2A recommendation for pemetrexed-based chemotherapy for unresectable malignant peritoneal mesothelioma or tunica vaginalis testis mesothelioma, relatively rarer forms of mesothelioma. Evidence for peritoneal mesothelioma, which accounts for about 30% of mesothelioma cases, consists of results from two open-label, expanded-access programs that found pemetrexed safe and active for this indication (Carteni, 2009; Jänne, 2005). To date, there are no published studies on pemetrexed's efficacy in tunica vaginalis testis which accounts for less than 1% of mesothelioma cases, though NCCN endorses it as a reasonable treatment approach for unresectable disease based on expert consensus.

Medical Policy

Healthcare Services Department

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Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J9304	Injection, pemetrexed, 10 mg [Pefexy]
J9305	Injection, pemetrexed, NOS, 10 mg [Alimta]
J9314	Injection, pemetrexed [Teva]
J9322	Injection, pemetrexed (bluepoint)
J9323	Injection, pemetrexed (hospira)
J9294	Injection, pemetrexed (Hospira)
J9296	Injection, pemetrexed (Accord)
J9297	Injection, pemetrexed (Sandoz)

ICD-10	Description
C34.00-C34.92	Malignant neoplasm of bronchus and lung
C37	Malignant neoplasm of thymus
C38.0-C38.8	Malignant neoplasm of heart, mediastinum and pleura
C45.0-C45.9	Mesothelioma
C48.0-C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C56.1-C56.9	Malignant neoplasm of ovary
C57.00-C57.9	Malignant neoplasm of other and unspecified female genital organs
C61	Malignant neoplasm of prostate
C65.1-C65.9	malignant neoplasm of renal pelvis
C66.1-C68.0	Malignant neoplasm of ureter, bladder, urethra
C78.00-C78.02	Secondary malignant neoplasm of lung
C78.2	Secondary malignant neoplasm of pleura
D15.0	Benign neoplasm of thymus
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
Z85.238	Personal history of other malignant neoplasm of thymus

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Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member’s medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Pemetrexed (Alimta®)

A. Criteria For Initial Approval *(Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient’s diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

- i. Individual has a diagnosis of malignant mesothelioma; **AND**
 - A. Individual is using in combination with cisplatin or carboplatin (Label, NCCN 2A); **OR**
 - B. Individual is using as a first-line therapy in combination with cisplatin or carboplatin **AND** bevacizumab (or bevacizumab biosimilar) (Label, NCCN 2A); **AND**
 - 1. Individual has an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; **AND**
 - 2. Individual does not have a history of hemoptysis or thrombosis; **AND**
 - 3. Disease presentation is unresectable;
 - OR**
 - C. Individual is using as single agent for subsequent therapy (NCCN 1); **AND**
 - 1. Pemetrexed was not administered as first-line; **OR**
 - 2. Pemetrexed was used as first-line with good sustained response;
 - OR**
 - D. Individual is using as single agent for first line systemic therapy;
- OR**
- ii. Individual has a diagnosis of recurrent, locally advanced, or metastatic non-squamous, non-small cell lung cancer (NSCLC); **AND**
 - A. Individual is using as a single agent after prior chemotherapy; **OR**
 - B. Individual is using as a first-line therapy in combination with platinum-based chemotherapy with or without bevacizumab (or bevacizumab biosimilar) (NCCN 2A); **OR**
 - C. Individual is using as second-line therapy in combination with platinum-based chemotherapy with or without bevacizumab (or bevacizumab biosimilar) if tyrosine-kinase inhibitor (TKI/anaplastic lymphoma kinase (ALK) targeted agent was given as first-line therapy (NCCN 1) ; **OR**
 - D. Individual is using for maintenance therapy when disease has not progressed following four cycles of platinum-based, first-line therapy; **OR**

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E. Individual is using in combination with pembrolizumab (Keytruda) and platinum chemotherapy for initial treatment and without presence of actionable molecular markers* (Label, NCCN 2A); **OR**

***Note:** Actionable molecular markers include EGFR, ALK, ROS1, BRAF, NTRK, MET and RET mutations. The NCCN panel recommends testing prior to initiating therapy to help guide appropriate treatment. If there is insufficient tissue to allow testing for all of these markers, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes (NCCN 2A).

F. Individual is using as continuous maintenance therapy until disease progression, if given first-line as part of Keytruda (pembrolizumab)/platinum chemotherapy/and pemetrexed regimen (NCCN 1); **OR**

G. Individual is using in combination with cemiplimab and platinum chemotherapy; **OR**

H. Individual is using in combination with tremelimumab, durvalumab, and platinum chemotherapy; **OR**

I. Individual is using in combination with bevacizumab as continuous maintenance therapy, if given first-line as part of bevacizumab/ platinum/and pemetrexed regimen (NCCN 2A); **OR**

J. Individual is using in combination with cemiplimab as continuous maintenance therapy, if given first-line as part of cemiplimab/ platinum/and pemetrexed regimen (NCCN 2A); **OR**

K. Individual is using in combination with durvalumab as continuous maintenance therapy if given first-line as part of tremelimumab/durvalumab/platinum/and pemetrexed regimen (NCCN 2A); **OR**

L. Individual is using as first-line therapy in combination with nivolumab, ipilimumab, and platinum-based chemotherapy and without presence of actionable molecular markers* (NCCN 2A); **OR**

***Note:** Actionable molecular markers include EGFR, ALK, ROS1, BRAF, NTRK, MET and RET mutations. The NCCN panel recommends testing prior to initiating therapy to help guide appropriate treatment. If there is insufficient tissue to allow testing for all these markers, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes (NCCN 2A).

M. Individual is using as adjuvant or neoadjuvant therapy in combination with platinum-based chemotherapy;

OR

iii. Individual is using as a single-agent therapy; **AND**

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- iv. Individual has one of the following (NCCN 2A):
 - A. Individual has a diagnosis for persistent or recurrent ovarian cancer; **OR**
 - B. Individual has a diagnosis for thymic cancer and thymomas and using as second-line therapy and beyond.

B. Criteria For Continuation of Therapy

- i. MMM considers continuation of Pemetrexed (Alimta®, Pefexy®) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of unacceptable toxicity or disease progression while on the current regimen, and the maximum duration of treatment has not been exceeded. The following information should be submitted for reauthorization:
 - A. A current oncology note documenting the patient’s response to treatment showing no progression of disease.
 - B. Current imaging studies and other objective measures, as appropriate, showing no progression of disease when compared with previous results.
- ii. Duration of treatment:
 - A. When used for initial treatment of locally advanced or metastatic non-squamous NSCLC, in combination with cisplatin: Up to 6 cycles (21-days each cycle).
 - B. For all other diagnosis: Until disease progression or unacceptable toxicity.

C. Authorization Duration

- i. Initial Approval Duration: Up to 6 months
- ii. Reauthorization Approval Duration: Up to 6 months

D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

- i. Individual has a diagnosis of squamous cell non-small cell lung cancer; OR
- ii. When the above criteria are not met and for all other indications.

Limits or Restrictions

A. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

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Pemetrexed (Alimta®, Pefexy®)	Recommended Dosing Schedule	Recommended Treatment Duration
Non-squamous NSCLC, in combination with Pembrolizumab, in patients with CrCl \geq 45 mL/min	500 mg/m ² i.v. on Day 1 of each 21-day cycle	Until Disease Progression or Unacceptable Toxicity.
For initial treatment of locally advanced or metastatic non-squamous NSCLC, in combination with cisplatin, in patients with CrCl \geq 45 mL/min	500 mg/m ² i.v. on Day 1 of each 21-day cycle	For up to 6 cycles.
For maintenance treatment of non-squamous NSCLC in patients with CrCl \geq 45 mL/min	500 mg/m ² i.v. on Day 1 of each 21-day cycle	Until Disease Progression or Unacceptable Toxicity.
For treatment of recurrent non-squamous NSCLC in patients with CrCl \geq 45 mL/min	500 mg/m ² i.v. on Day 1 of each 21-day cycle	Until Disease Progression or Unacceptable Toxicity.
Mesothelioma treatment, in patients with CrCl \geq 45 mL/min	500 mg/m ² i.v. on Day 1 of each 21-day cycle	Until Disease Progression or Unacceptable Toxicity.
Exceptions		
- There is no recommended dose for patients whose creatinine clearance is less than 45 mL/min		

Reference Information

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 - a. Central Nervous System Cancers. V2.2022. Revised September 29, 2022.
 - b. Malignant Pleural Mesothelioma. V1.2023. Revised December 15, 2022.
 - c. Non-Small Cell Lung Cancer. V1.2023. Revised December 22, 2022.
 - d. Ovarian Cancer, including fallopian tube cancer and primary peritoneal cancer. V5.2022. Revised September 16, 2022.
 - e. Thymomas and Thymic Carcinomas. V1.2023. Revised December 15, 2022.
11. Patel JD, Socinski MA, Garon EB, et al. PointBreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2013; 31(34):4349-4357
12. Raizer JJ, Rademaker A, Evens AM, et al. Pemetrexed in the treatment of relapsed/refractory primary central nervous system lymphoma. *Cancer*. 2012; 118(15):3743-3748.
13. Zhang L, Ou W, Liu Q, Li N, Liu L, Wang S. Pemetrexed plus carboplatin as adjuvant chemotherapy in patients with curative resected non-squamous non-small cell lung cancer. *Thorac Cancer*. 2014;5(1):50-56. doi:10.1111/1759-7714.12058. Available at: <https://onlinelibrary.wiley.com/doi/full/10.1111/1759-7714.12058>. Accessed January 11, 2021.

Federal and state laws or requirements, contract language, and Plan utilization management programs or policies may take precedence over the application of this clinical criteria.

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Policy History

Revision Type	Summary of Changes	P&T Approval Date	MPCC Approval Date
Policy Inception	Elevance Health’s Medical Policy adoption.	N/A	11/30/2023
Select Review	Update statement for criteria for initial approval: Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient’s diagnosis for the drug and confirming that the patient has met all approval criteria.	3/25/2024	5/9/2024

Revised: 11/19/2023