Medical Drug Clinical Criteria

Subject:	Pemetrexed ~~(Alimta, Axtle, Pemfexy, Pemrydi)~~		
Document #:	CC-0094	**Publish Date:**	~~02/03/2025~~07/01/2025
Status:	Revised	**Last Review Date:**	~~12/09/2024~~05/16/2025

Table of Contents

Overview

This document addresses the use of pemetrexed agents, including Alimta (pemetrexed disodium), Pemfexy (pemetrexed) and Pemrydi RTU (pemetrexed), Axtle (pemetrexed dipotassium) which are folate analog metabolic inhibitors. They work by inhibiting folate-dependent metabolic processes which disrupts cell replication. Pemrydi is a ready to use presentation of pemetrexed for injection.

The FDA approved indications for pemetrexed includes 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).
- 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 Alimta, Axtle, Pemfexy, and Pemrydi are not 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 cervical cancer, central nervous system lymphomas, 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 Pemfexy for any indication, including the use in NSCLC in combination with pembrolizumab and platinum therapy for initial treatment. Pemrydi is not yet addressed by NCCN.

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 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.

Clinical Criteria

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 Agents (Alimta, Axtle, Pemfexy, Pemrydi)

Requests for Pemetrexed Agents (Alimta, Axtle, Pemfexy, Pemrydi) may be approved if the following criteria are met:

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~~ platinum-based chemotherapy AND bevacizumab (or bevacizumab biosimilar) (Label, NCCN ~~2A~~1); ~~**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;~~

Formatted: Add space between paragraphs of the same style

OR

C. Individual is using as a first-line therapy in combination with platinum-based chemotherapy and pembrolizumab (NCCN 1);

OR

~~C.~~D. 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.~~E. Individual is using as single agent for first line systemic therapy (NCCN 2A);

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 or induction 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 (first-line chemotherapy) 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.~~C. Individual is using as a single agent for maintenance therapy ~~when disease has not progressed following four cycles of platinum-based, first-line therapy; **OR**~~

~~E.~~D. 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**

~~F.~~E. 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.~~F. Individual is using in combination with cemiplimab and platinum chemotherapy; **OR**

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

~~I.~~H. 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.~~I. 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.~~J. 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.~~K. 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**

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

M. Individual is using in combination with Rybrevant (amivantamab-vmjw) and carboplatin (NCCN 1); **OR**

N. Individual is using as first-line therapy for EGFR exon 19 deletion or exon 21 L858R recurrent, advanced, or metastatic disease in combination with osimertinib and platinum-based chemotherapy (NCCN 1, 2A);

OR

III. Individual has a diagnosis of for EGFR mutation positive non-small cell lung cancer with leptomeningeal metastases; **AND**

IV. Pemetrexed is being administered intrathecally;

OR

V. Individual has a diagnosis of non-nasopharyngeal head and neck cancer (NCCN 2A);

OR

~~I.~~VI. Individual is using as a single-agent therapy; **AND**

~~II.~~VII. 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~~; **OR**

C. Individual is using pemetrexed as second-line or subsequent therapy for cervical cancer; OR

D. Individual has a diagnosis for primary central nervous system lymphoma; **OR**

~~D.~~E. Individual is using pemetrexed as second-line or subsequent therapy for vaginal cancer.

Pemetrexed Agents (Alimta, Axtle, Pemfexy, Pemrydi) may not be approved for the following:

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.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement

Formatted: Font: Bold

Formatted: Normal, Indent: Left: 0.5", No bullets or numbering, Tab stops: 0.5", Left + Not at 0.75"

Formatted: Font: (Default) Arial, 9 pt

Formatted: Font: Bold

Formatted: Indent: Left: 0.5", Numbered + Level: 1 + Numbering Style: A, B, C, … + Start at: 3 + Alignment: Left + Aligned at: 0.75" + Indent at: 1"

Formatted: Indent: Left: 0.5", Numbered + Level: 1 + Numbering Style: A, B, C, … + Start at: 13 + Alignment: Left + Aligned at: 0.25" + Indent at: 0.5"

Formatted: No underline

Formatted: No underline

Formatted: Don't add space between paragraphs of the same style, Numbered + Level: 1 + Numbering Style: I, II, III, … + Start at: 1 + Alignment: Right + Aligned at: 0.25" + Indent at: 0.5"

Formatted: Font: (Default) Arial, 9 pt, Underline

Formatted: Font: Bold

Formatted: Normal, No bullets or numbering

Formatted: Numbered + Level: 1 + Numbering Style: I, II, III, … + Start at: 1 + Alignment: Right + Aligned at: 0.25" + Indent at: 0.5"

Formatted: Font: Bold

policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J9304	Injection, pemetrexed (Pemfexy), 10 mg ~~Injection, pemetrexed, 10 mg [Pemfexy]~~
J9305	Injection, pemetrexed, NOS, 10 mg [Alimta]
J9314	Injection, pemetrexed (Teva), not therapeutically equivalent to J9305, 10 mg
J9322	Injection, pemetrexed (BluePoint), not therapeutically equivalent to J9305, 10 mg
J9323	Injection, pemetrexed ditromethamine, 10 mg
J9324	Injection, pemetrexed (Pemrydi rtu), 10 mg
J9292	Injection, pemetrexed dipotassium, 10 mg [Avyxa]~~Injection, pemetrexed (Avyxa), not therapeutically equivalent to J9035, 10 mg~~
J9294	Injection, pemetrexed (Hospira), not therapeutically equivalent to J9305, 10 mg
J9296	Injection, pemetrexed (Accord), not therapeutically equivalent to J9305, 10 mg
J9297	Injection, pemetrexed (Sandoz), not therapeutically equivalent to J9305, 10 mg
J9999	Not otherwise classified, antineoplastic drugs [Axtle]
C9399	Unclassified drugs or biologicals [Axtle]

ICD-10 Diagnosis

C00.0-C06.9	Malignant neoplasm of lip, tongue, and oral cavity
C09.0-C10.9	Malignant neoplasm of tonsil, oropharynx
C12-C14.8	Malignant neoplasm of pyriform sinus, hypopharynx, other and ill-defined sites in the lip, oral cavity and pharynx
C31.0-C32.9	Malignant neoplasm of accessory sinuses, larynx
C33	Malignant neoplasm of trachea
C34.00-C34.92	Malignant neoplasm of bronchus and lung
C37	Malignant neoplasm of thymus
C38.4	Malignant neoplasm of pleura
C45.0-C45.9	Mesothelioma
C48.0-C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C52	Malignant neoplasm of vagina
C53.0-C53.9	Malignant neoplasm of cervix uteri
C56.1-C56.9	Malignant neoplasm of ovary
C57.00-C57.9	Malignant neoplasm of other and unspecified female genital organs
~~C78.00-C78.02~~	~~Secondary malignant neoplasm of lung~~
~~C78.2~~	~~Secondary malignant neoplasm of pleura~~
C76.0	Malignant neoplasm of head, face and neck
C79.32	Secondary malignant neoplasm of cerebral meninges
C83.390	Primary central nervous system lymphoma
D15.0	Benign neoplasm of thymus
Z85.118	Personal history of other malignant neoplasm of bronchus and lung

Document History

Revised: 05/16/2025
Document History:

- 05/16/2025 – Annual Review: update mesothelioma criteria, update NSCLC criteria, and non-nasopharyngeal head and neck cancer, add vaginal cancer, update thymomas and thymic carcinomas. Coding Reviewed: Updated description for HCPCS J9292 effective 7/1/25. Updated description for J9304. Added ICD-10-CM C00.0-C06.9, C09.0-C10.9, C12-C14.8, C31.0-C32.9, C52, C76.0. Removed C78.00-C78.02, C78.2.

- 12/09/2024 – Select Review: Add Axtle to criteria. Coding Reviewed: Added HCPCS NOC J9999 and C9399 for Axtle.
- 12/3/2024 – Coding update only: Add HCPCS J9292 effective 1/1/25. Add ICD-10-CM C33, C53.0-C53.9, C79.32, C83.390. Removed ICD-10-CM C38.0-C38.8 code range and add C38.4. Remove ICD-10-CM C61, C65.1-C65.9, C66.1-C68.0.
- 06/10/2024 – Select Review: Add combination use with Rybrevant and carboplatin for Non-small cell lung cancer, formatting. Coding Reviewed: Updated coding description for HCPCS J9314, J9322, J9323, J9294, J9296, J9297.
- 02/23/2024 – Annual Review: Add Pemrydi, Add induction therapy for Non-small cell lung cancer, cervical cancer, primary central nervous system lymphoma and NSCLC CNS metastases. Coding Reviewed: No changes.
- 02/24/2023 – Annual Review: Add indication for pleural mesothelioma, add cemiplimab/platinum and durvalumab/tremelimumab/platinum combinations for NSCLC. Coding Reviewed: No changes. Effective 7/1/2023 Added HCPCS J9322, J9323, J9294, J9296, J9297. Effective 1/1/2024 Added HCPCS J9324.
- 02/25/2022 – Annual Review: No changes. Coding Reviewed: No changes. Effective 1/1/2023 Added HCPCS J9314.
  02/19/2021 – Annual Review: Update criteria to add new agent Pemfexy (pemetrexed) to document. Update NSCLC criteria to allow use in recurrent disease, and add use in combination with nivolumab, ipilimumab, *and* platinum-based chemotherapy per guidelines. Update NSCLC criteria to specify any actionable molecular marker with a note to further expand on definition and marker testing. Add indication for use as adjuvant or neoadjuvant therapy in NSCLC. Wording and formatting updates. Coding Reviewed: Added J9304.
- 08/21/2020 – Select Review: Update criteria for first line use in NSCLC with Keytruda in individuals with negative or unknown EGFR, ALK, ROS1, and BRAF mutations. Coding Reviewed: No changes.
- 02/21/2020 – Annual Review: Update criteria to add use in malignant mesothelioma as single agent, subsequent therapy per NCCN recommendations. Update approvable criteria to remove use in urothelial carcinoma per NCCN update. Update non-approvable criteria for consistency. Add notation in criteria for interchangeability with bevacizumab biosimilar for mesothelioma and NSCLC indications. Wording and formatting changes. Coding Reviewed: Added ICD-10-CM C37, C45.0-C45.9, C56.1-C56.9
- 08/16/2019 – Select Review: Wording and formatting changes for clarity.
- 05/17/2019 – Annual Review: First review of Alimta (pemetrexed). Update Alimta criteria for consistency to include FDA label update for use in combination with pembrolizumab (Keytruda) and platinum chemotherapy for metastatic non-squamous NSCLC as initial treatment in those without EGFR or ALK genomic tumor aberrations. Update Alimta criteria for consistency to include NCCN recommendations for combination use of Alimta with or without bevacizumab in non-squamous NSCLC. Wording and formatting changes. Coding reviewed: Revised code: No change.

References

1. Barlesi F, Scherpereel A, Rittmeyer A, et al. Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced nonsquamous non-small-cell lung cancer: AVAPERL (MO22089). J Clin Oncol. 2013; 31(24):3004-3011
2. Carteni G, Manegold C, Garcia GM, et al. Malignant peritoneal mesothelioma-Results from the International Expanded Access Program using pemetrexed alone or in combination with a platinum agent. Lung Cancer. 2009; 64(2):211-218.
3. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2025. URL: http://www.clinicalpharmacology.com. Updated periodically.
4. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Updated periodically
5. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
6. Jänne PA, Wozniak AJ, Belani CP, et al. Open-label study of pemetrexed alone or in combination with cisplatin for the treatment of patients with peritoneal mesothelioma: outcomes of an expanded access program. Clin Lung Cancer. 2005; 7(1):40-46.
7. Kenmotsu H, Yamamoto N, Yamanaka T, et al. Randomized Phase III Study of Pemetrexed Plus Cisplatin Versus Vinorelbine Plus Cisplatin for Completely Resected Stage II to IIIA Nonsquamous Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2020;38(19):2187-2196. doi:10.1200/JCO.19.02674
8. Kreuter M, Vansteenkiste J, Fischer JR, et al. Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine: the TREAT study. *Ann Oncol*. 2013;24(4):986-992. doi:10.1093/annonc/mds578
9. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2025; Updated periodically.
10. NCCN Clinical Practice Guidelines in Oncology™. © 2025 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed April 4, 2025.
    a. Central Nervous System Cancers. V4.2024. Revised February 10, 2025.
    b. Cervical Cancer. V3.2025. Revised January 21, 2025.
    c. Head and Neck Cancers. V2.2025. Revised January 17, 2025.
    d. Mesothelioma: Peritoneal. V2.2025. Revised January 14, 2025.
    e. Non-Small Cell Lung Cancer. V3.2025. Revised January 14, 2025.
    f. Ovarian Cancer, including fallopian tube cancer and primary peritoneal cancer. V1.2025. Revised March 5, 2025.
    g. Thymomas and Thymic Carcinomas. V1.2025. Revised October 30, 2024
    h. Vaginal Cancer. V5.2025. Revised February 28, 2025.
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 polices may take precedence over the application of this clinical criteria.