Clinical Policy: Pemetrexed (Alimta, Pemfexy, Axtle)

Reference Number: PA.CP.PHAR.368
Effective Date: 10/2017
Last Review Date: 01/2026

Description
Pemetrexed (Alimta®, Pemfexy®, Axtle™) is an antifolate antineoplastic agent.

FDA Approved Indication(s)
Alimta is indicated for:

- In combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.
  Alimta and Pemfexy are indicated:
- 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.
  Limitations of Use: Alimta and Pemfexy are not indicated for the treatment of patients with squamous cell, non-small cell lung cancer.
- 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.

Policy/Criteria
Provider must submit documentation (which may include office chart notes and lab results) supporting that member has met all approval criteria

It is the policy of PA Health & Wellness that Alimta, Pemfexy and Axtle are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Non-Small Cell Lung Cancer or Mesothelioma (must meet all)**:**

1. One of the following diagnoses (a or b):
   a. Non-squamous NSCLC;
   b. One of the following malignant mesotheliomas (i, ii, iii, or iv):
      i. Pleural;
      ii. Peritoneal (off-label);
      iii. Pericardial (off-label);
      iv. Tunica vaginalis testis (off-label);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;

4. If Alimta, Pemfexy or Axtle is requested, member must use generic pemetrexed, unless contraindicated or clinically significant adverse effects are experienced;
5. Request meets one of the following (a or b):
   a. Dose does not exceed 500mg/m^2 administered every 21 days;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

B. Thymomas or Thymic Carcinomas (off-label) (must meet all)**:**
1. Diagnosis of thymomas or thymic carcinomas;
2. Prescribed by or in consultation with an oncologist:
3. Age ≥ 18 years;
4. One of the following (a or b):
   a. Prescribed as second line therapy *(initial treatment may include surgery, radiation therapy, chemotherapy)*;
   b. Member unable to tolerate first-line combination regimens;
5. Prescribed as a single agent;
6. If Alimta, Pemfexy or Axtle is requested, member must use generic pemetrexed, unless contraindicated or clinically significant adverse effects are experienced;
7. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

C. Ovarian/Fallopian Tube/Primary Peritoneal Cancer (off-label) (must meet all)**:**
1. Diagnosis of ovarian, fallopian tube, or primary peritoneal cancer;
2. Prescribed by or in consultation with an oncologist:
3. Age ≥ 18 years;
4. Disease is persistent or recurrent;
5. Prescribed as a single agent;
6. If Alimta, Pemfexy or Axtle is requested, member must use generic pemetrexed, unless contraindicated or clinically significant adverse effects are experienced;
7. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

D. Central Nervous System Lymphoma (off-label) (must meet all)**:**
1. Diagnosis of one of the following (a, b or c):
   a. Primary central nervous system (CNS) lymphoma;
   b. Leptomeningeal metastases;
   c. Extensive or limited brain metastases;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. For primary CNS lymphoma, prescribed as a single agent for one of the following (a or b):

a. Relapsed or refractory disease;
b. Induction therapy if member is unsuitable for or intolerant to high-dose methotrexate;

5. If Alimta, Pemfexy or Axtle is requested, member must use generic pemetrexed, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

E. Cervical Cancer or Vaginal Cancer (off-label) (must meet all)**:**

1. Diagnosis of cervical cancer or vaginal cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years
4. Prescribed as a single agent as second-line or subsequent therapy;
5. If Alimta, Pemfexy or Axtle is requested, member must use generic pemetrexed, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

F. Non-Nasopharyngeal Cancer (off-label) (must meet all):

1. Diagnosis of non-nasopharyngeal cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. If Alimta, Pemfexy or Axtle is requested, member must use generic pemetrexed, unless contraindicated or clinically significant adverse effects are experienced;
5. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

G. Thyroid Cancer (off-label) (must meet all):

1. Diagnosis of thyroid carcinoma that is one of the following types (a or b):
   a. Differentiated (i.e., papillary, follicular, oncocytic);
   b. Anaplastic;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease has progressed following prior treatment (*see Appendix B*);
5. Prescribed in combination with carboplatin;
6. One of the following (a or b):
   a. For differentiated thyroid carcinoma: Disease is unresectable, recurrent, persistent, or metastatic;
   b. For anaplastic thyroid carcinoma: Disease is stage IVC (metastatic);
7. For papillary or follicular carcinoma, disease is radioactive iodine (RAI)-refractory;

8. If Alimta, Pemfexy, or Axtle is requested, member must use generic pemetrexed, unless contraindicated or clinically significant adverse effects are experienced;
9. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

H. Other diagnoses/indications

1. Refer to PA.CP.PMN.53 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**

1. Currently receiving medication via PA Health &Wellness benefit or member has met all initial approval criteria or the Continuity of Care Policy (PA.PHARM.01) applies;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a or b):
   a. New dose does not exceed 500mg/m^2 administered every 21 days;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via PA Health &Wellness benefit or member has met all initial approval criteria or the Continuity of Care Policy (PA.PHARM.01) applies; **Approval duration: Duration of request or 6 months (whichever is less)**; or
2. Refer to PA.CP.PMN.53 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy – PA.CP.PMN.53 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALK: anaplastic lymphoma kinase
CNS: central nervous system
EGFR: epidermal growth factor receptor
FDA: Food and Drug Administration
NCCN: National Comprehensive Cancer Network
NSCLC: non-small cell lung cancer

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Lenvima® (lenvatinib)	Differentiated thyroid carcinoma: 24 mg PO QD	24 mg/day
sorafenib (Nexavar®)	Differentiated thyroid carcinoma: 400 mg PO BID	800 mg/day
Mekinist® (trametinib)/ Tafinlar® (dabrafenib), Rozlytrek® (entrectinib), Vitrakvi® (larotrectinib), Gavreto® (pralsetinib), doxorubixin, paclitaxel	Anaplastic carcinoma: Varies	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): history of severe hypersensitivity reaction to pemetrexed
- Boxed warning(s): none reported

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
NSCLC	500 mg/m^2 IV on Day 1 of each 21-day cycle as a single agent or in combination with cisplatin, or carboplatin and pembrolizumab.	500 mg/m^2 IV infusion every 21 days
Malignant pleural mesothelioma	500 mg/m^2 IV on Day 1 of each 21-day cycle in combination with cisplatin.	

VI. Product Availability

Drug Name	Availability
Alimta	Single-dose vial for injection: 100 mg, 500 mg
Pemfexy	Multi-dose vial for injection: 500 mg
Axtle	Single-dose vials for injection: 100 mg, 500 mg (equivalent to 118.3 mg, 591.5 mg pemetrexed dipotassium)

VII. References

1. Alimta Prescribing Information. Indianapolis, IN: Eli Lilly Pharmaceuticals; May 2023. Available at: https://uspl.lilly.com/alimta/alimta.html#. Accessed November 6, 2025.
2. Pemfexy Prescribing Information. Woodcliff Lake, NJ: Eagle Pharmaceuticals, Inc. June 2020. Available at: www.pemfexy.com. Accessed November 6, 2025.
3. Axtle Prescribing Information. New Jersey, USA: Avyxa Pharma, LLC; October 2025. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/210661s004lbl.pdf. Accessed November 6, 2025.
4. National Comprehensive Cancer Network Drugs and Biologics Compendium. http://www.nccn.org/professionals/drug_compendium. Accessed November 19, 2025.

5. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer Version 2.2026. Available at https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed November 19, 2025.
6. National Comprehensive Cancer Network. Mesothelioma: Pleural Version Version 2.2026. Available at https://www.nccn.org/professionals/physician_gls/pdf/meso_pleural.pdf. Accessed November 19, 2025.
7. National Comprehensive Cancer Network. Thymomas and Thymic Carcinomas Version 1.2026. Available at https://www.nccn.org/professionals/physician_gls/pdf/thymic.pdf.. Accessed November 19, 2025.
8. National Comprehensive Cancer Network. Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer Version 3.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed November 19, 2025.
9. National Comprehensive Cancer Network. Central Nervous System Version 3.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed November 19, 2025.
10. National Comprehensive Cancer Network. Mesothelioma: Peritoneal Version 2.2026. Available at: https://www.nccn.org/professionals/physician_gls/pdf/meso_peritoneal.pdf. Accessed November 19, 2025.
11. National Comprehensive Cancer Network Guidelines. Cervical Cancer Version 2.2026. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. Accessed November 22, 2025.
12. National Comprehensive Cancer Network Guidelines. Head and Neck Cancers Version 1.2026. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. Accessed December 18, 2025.
13. National Comprehensive Cancer Network Guidelines. Thyroid Carcinomas Version 1.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf. Accessed November 19, 2025.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J9304	Injection, pemetrexed (pemfexy), 10 mg
J9305	Injection, pemetrexed, not otherwise specified, 10 mg
J9314	Injection, pemetrexed (teva) not therapeutically equivalent to J9305, 10 mg
J9292	Injection, pemetrexed dipotassium, 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
J9322	Injection, pemetrexed (bluepoint) not therapeutically equivalent to J9305, 10 mg

HCPCS Codes	Description
J9323	Injection, pemetrexed ditromethamine, 10 mg
J9324	Injection, pemetrexed (pemrydi rtu), 10 mg

Reviews, Revisions, and Approvals	Date
1Q 2019 annual review; age added; new NSCLC labeled indication added to indication section; bladder cancer relabeled as UC, methotrexate trial removed from CNS lymphoma and FDA approved treatments removed from ovarian cancer to encompass NCCN uses; references reviewed and updated.	01/2019
1Q 2020 annual review; added updated FDA indication: NSCLC without EGFR or ALK gene mutation in combination with platinum chemotherapy and pembrolizumab; this is already a covered use, therefore no modification to criteria was required; references reviewed and updated.	01/2020
1Q 2021 annual review: induction therapy offered for primary CNS lymphoma per NCCN; urothelial carcinoma off-label use removed per NCCN; references reviewed and updated.	01/2021
1Q 2022 annual review: added other sources of malignant mesotheliomas per NCCN; added criterion for use as single-agent therapy for thymomas/thymic carcinomas, ovarian/fallopian tube/primary peritoneal cancers, and primary central nervous system lymphomas per NCCN; references reviewed and updated.	01/2022
1Q 2023 annual review: for thymomas/thymic carcinomas added option for members who cannot tolerate first-line combination regimens per NCCN; added criteria for cervical cancer per NCCN; updated product availability of Pemfexy; added redirection to generic pemetrexed; updated HCPCS codes. references reviewed and updated.	01/2023
1Q 2024 annual review: for CNS, added option for treatment of leptomeningeal metastases per NCCN; removed HCPCS codes [J9321]; references reviewed and updated.	01/2024
1Q 2025 annual review: for cervical cancer, removed hematologist as prescriber option; added off-label indications for vaginal cancer and non-nasopharyngeal cancers per NCCN; for continued therapy revised language from “has had at least one dose in the last 90 days” to our standard language of “received this medication for at least 30 days”; HCPCS code added [J9292].updated HCPCS code descriptions for [J9297 and J9323]; references reviewed and updated.	01/2025
1Q 2026 annual review: RT4: added newly approved Axtle to the policy; RT4: updated indication for Axtle to include combination with Keytruda and a platinum for NSCLC per PI; added off-label indication of thyroid carcinoma per NCCN Compendium; updated HCPCS code description for J9292; extended initial approval duration from 6 to 12 months for this maintenance medication for a chronic condition; references reviewed and updated.	01/2026