Clinical Policy: Pemetrexed (Alimta, Pemfexy, Axtle)

Reference Number: CP.PHAR.368
Effective Date: 10.31.17
Last Review Date: 02.26
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

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

FDA Approved Indication(s)

Alimta, Pemfexy, and Axtle are indicated:

- 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.
- 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, Pemfexy, and Axtle are not indicated for the treatment of patients with squamous cell, NSCLC.
- 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 (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® 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. Diagnosis of one of the following (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 500 mg per m^2 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*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration
Medicaid/HIM – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

B. Thymoma or Thymic Carcinoma (off-label) (must meet all)**:**
1. Diagnosis of thymoma or thymic carcinoma;
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*).*

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:
Medicaid/HIM – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

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).*

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:
Medicaid/HIM – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

D. Central Nervous System Lymphoma (off-label) (must meet all)**:**
1. Diagnosis of one of the following (a or b):
   a. Primary central nervous system (CNS) lymphoma;
   b. Leptomeningeal 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*).*
   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:
Medicaid/HIM – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

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*).*
   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:
Medicaid/HIM – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

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*).*
   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:
Medicaid/HIM – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

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*).*
   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:
Medicaid/HIM – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

H. Other diagnoses/indications (must meet 1 or 2)**:**
a. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   i. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace and CP.PMN.255 for Medicaid; or
   ii. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace and CP.PMN.16 for Medicaid; or
b. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Currently receiving medication via Centene benefit or documentation supports that member has received Alimta, Pemfexy, or Axtle for a covered indication and has received this medication for at least 30 days;
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 500 mg/m^2 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*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:
Medicaid/HIM – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid.

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 policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, 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
RAI: radioactive iodine

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, in combination with cisplatin, or in combination with platinum therapy 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 vials for injection: 100 mg, 500 mg
Pemfexy	Multi-dose vial for injection: 500 mg/20 mL
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#pi. Accessed November 6, 2025.
2. Pemfexy Prescribing Information. Woodcliff Lake, NJ: Eagle Pharmaceuticals, Inc. December 2022. 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. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed November 19, 2025.
5. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer Version 11.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed November 19, 2025.
6. National Comprehensive Cancer Network. Mesothelioma: Pleural Version 2.2024. 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 1.2025. 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 3.2024. 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 3.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. November 19, 2025.
10. National Comprehensive Cancer Network. Mesothelioma: Peritoneal Version 3.2024. 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 4.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. Accessed November 19, 2025
12. National Comprehensive Cancer Network Guidelines. Head and Neck Cancers Version 5.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. Accessed November 19, 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

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

Reviews, Revisions, and Approvals	Date	P&T Approval Date
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.	11.13.21	02.22
Added redirection to generic pemetrexed; updated HCPCS codes.	05.31.22	
Template changes applied to other diagnoses/indications.	09.22.22	
1Q 2023 annual review: for thymomas/thymic carcinomas added option for members who cannot tolerate first-line combination regimens per NCCN; updated product availability of Pemfexy; references reviewed and updated. RT4: updated FDA indication for Pemfexy to include combination use with pembrolizumab and platinum chemotherapy for NSCLC without EGFR or ALK gene mutation per updated PI; references reviewed and updated. Updated HCPCS code [J9314].	01.09.23	02.23
Added HCPCS codes [J9294, J9296, J9297, J9321, J9322, J9323]	05.24.23	
Added HCPCS code [J9324]	10.26.23	
1Q 2024 annual review: for CNS, added option for treatment of leptomeningeal metastases per NCCN; added criteria for cervical cancer per NCCN; removed HCPCS codes [J9321]; references reviewed and updated.	10.16.23	02.24
HCPCS code added [J9292].	11.06.24	
1Q 2025 annual review: added Commercial line of business; 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"; updated HCPCS code descriptions for [J9297 and J9323]; references reviewed and updated. RT4: added newly approved Axtle to the policy.	12.13.24	02.25
RT4: updated indication for Axtle to include combination with Keytruda and a platinum for NSCLC per PI; added off-label	10.14.25	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
indication of thyroid carcinoma per NCCN Compendium; updated HCPCS code description for J9292.		
1Q 2026 annual review: no significant changes; extended initial approval duration from 6 to 12 months for this maintenance medication for a chronic condition; references reviewed and updated.	11.06.25	02.26

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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