# Evolent Clinical Guideline 3190 for Alimta/Pemfexy/Axtle/Pemrydi™ (pemetrexed)

| Guideline Number: | Applicable Codes | |
|---|---|---|
| Evolent_CG_3190 | | |
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| **Original Date:** | **Last Revised Date:** | **Implementation Date:** |
| July 2011 | October 2025 | October 2025 |

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# STATEMENT

## Purpose

To define and describe the accepted indications for Alimta/Pemfexy/Axtle/Pemrydi (pemetrexed) usage in the treatment of cancer, including FDA approved indications, and off-label indications.

Evolent is responsible for processing all medication requests from network ordering providers. Medications not authorized by Evolent may be deemed as not approvable and therefore not reimbursable.

The use of this drug must be supported by one of the following: FDA approved product labeling, CMS-approved compendia, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) clinical guidelines, or peer-reviewed literature that meets the requirements of the CMS Medicare Benefit Policy Manual Chapter 15.

# INDICATIONS

**Continuation requests for a not-approvable medication shall be exempt from this Evolent policy provided**

- The member has not experienced disease progression on the requested medication AND
- The requested medication was used within the last year without a lapse of more than 30 days of having an active authorization AND
- Additional medication(s) are not being added to the continuation request.

## Malignant Pleural Mesothelioma

- The member has malignant pleural mesothelioma and Alimta/Pemfexy/Axtle/Pemrydi (pemetrexed) may be used in ONE of the following:
  - In combination with cisplatin/carboplatin for stage I-IIIA clinically operable disease OR
  - In combination with Keytruda (pembrolizumab) and cisplatin/carboplatin as first-line treatment of unresectable advanced or metastatic disease OR
  - As first line therapy for unresectable or metastatic disease as a single agent or in combination with cisplatin or carboplatin with or without bevacizumab OR
  - As subsequent therapy as a single agent (if not previously used in the first line setting).
- NOTE: Per Evolent Policy, J9304 Pemfexy (pemetrexed) is not supported for the treatment of malignant pleural mesothelioma. This recommendation is based on the lack of Level 1 Evidence (randomized clinical trial and/or meta-analyses) to show superior outcomes with one pemetrexed product over another.

## Non-Small Cell Lung Cancer (NSCLC)

- The member has recurrent or metastatic non-squamous NSCLC and Alimta/Pemfexy/Axtle/Pemrydi (pemetrexed) may be used for ANY of the following:

- First line therapy in combination with carboplatin/cisplatin OR
- First line in combination with carboplatin/cisplatin + Keytruda (pembrolizumab) for EGFR negative and ALK negative disease OR
- First line in combination with Rybrevant (amivantamab-vmjw) + carboplatin for EGFR exon 20 insertion mutations OR
- Subsequent therapy in combination with carboplatin/cisplatin OR
- Subsequent therapy in combination with Rybrevant (amivantamab-vmjw) + carboplatin for EGFR exon 19 deletions or exon 21 L858R substitution mutations OR
- Subsequent therapy as a single agent OR
- Maintenance therapy as a single agent after response or stable disease following first-line chemotherapy or maintenance therapy in combination with pembrolizumab following first-line therapy with [pembrolizumab + pemetrexed + cisplatin/carboplatin] OR
- First line therapy in combination with Imfinzi (durvalumab), Imjudo (tremelimumab) and platinum-based chemotherapy for up to 4 cycles in adult members who have not received prior systemic therapy for metastatic or Stage IV NSCLC and the tumor is negative for EGFR and ALK, regardless of PD-L1 expression. This may be followed by maintenance therapy with Imfinzi (durvalumab), 1 dose of Imjudo (tremelimumab) and optional histology-based pemetrexed.

- NOTE 1: Per Evolent Policy, the following regimens are not supported based on the lack of Level 1 Evidence (randomized clinical trial and/or meta-analyses) demonstrating superior outcomes compared to Evolent recommended alternatives agents/regimens, including but not limited to regimens at **Evolent Pathways**:
  - Bevacizumab + Carboplatin/Cisplatin + Pemetrexed followed by maintenance Bevacizumab + Pemetrexed
  - Nivolumab + Ipilimumab + Carboplatin/Cisplatin + Pemetrexed followed by maintenance Nivolumab + Ipilimumab (for a PDL-1 expression 1% or higher)
- NOTE 2: Per Evolent Policy, J9304 Pemfexy (pemetrexed) is not supported for the treatment of NSCLC. This recommendation is based on the lack of Level 1 Evidence (randomized clinical trial and/or meta-analyses) to show superior outcomes with one pemetrexed product over another.

# CONTRAINDICATIONS/WARNINGS

- Contraindications
  - Severe hypersensitivity to pemetrexed or any component of the formulation
- Warnings
  - Bone marrow suppression
    - Pemetrexed may cause severe myelosuppression, including anemia, neutropenia, thrombocytopenia, and/or pancytopenia; myelosuppression is often dose-limiting. Severe myelosuppression may require blood transfusion

or may lead to neutropenic infection. Prophylactic folic acid and vitamin $B_{12}$ supplements are necessary to reduce hematologic toxicity, febrile neutropenia, and infection; the risk for myelosuppression is higher in patients who did not receive vitamin supplementation.

# EXCLUSION CRITERIA

- Dosing exceeds single dose limit of Alimta/Pemfexy/Axtle/Pemrydi (pemetrexed) 500 $mg/m^2$.
- Disease progression on Pemetrexed or Pemetrexed containing regimen.
- Use of Alimta/Pemfexy/Axtle/Pemrydi (pemetrexed) for squamous cell NSCLC.
- Investigational use of Alimta/Pemfexy/Axtle/Pemrydi (pemetrexed) with an off-label indication that is not sufficient in evidence or is not generally accepted by the medical community. Sufficient evidence that is not supported by CMS recognized compendia or acceptable peer reviewed literature is defined as any of the following:
    - Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
    - Whether the administered chemotherapy/biologic therapy/immune therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.
    - Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients. Generally, the definition of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of less than 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.
    - Whether the experimental design, in light of the drugs and conditions under investigation, is appropriate to address the investigative question. (For example, in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover).
    - That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
    - That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
    - That abstracts (including meeting abstracts) without the full article from the approved peer-reviewed journals lack supporting clinical evidence for determining accepted uses of drugs.

# CODING AND STANDARDS

## Codes

- 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
- 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
- J9322 - Injection, pemetrexed (bluepoint), not therapeutically equivalent to j9305, 10 mg
- J9323 - Injection, pemetrexed ditromethamine, 10 mg
- J9324 - Injection, pemetrexed (pemrydi rtu), 10 mg

## Applicable Lines of Business

| | |
|---|---|
| ☐ | CHIP (Children's Health Insurance Program) |
| ☒ | Commercial |
| ☒ | Exchange/Marketplace |
| ☒ | Medicaid |
| ☐ | Medicare Advantage |

# POLICY HISTORY

| Date | Summary |
|---|---|
| October 2025 | • Converted to new Evolent guideline template<br>• This guideline replaces UM ONC_1130 Alimta or Pemfexy (pemetrexed)<br>• Added new brand names “Axtle” and “Pemrydi” to relevant sections<br>• Updated NSCLC indication to allow maintenance therapy with durvalumab +/- pemetrexed after first-line therapy for recurrent, advanced, or metastatic disease with platinum-based chemotherapy, tremelimumab, and durvalumab if restaging shows stability or response<br>• Updated exclusion criteria<br>• Updated references |
| October 2024 | • Added use with pembrolizumab and platinum chemotherapy to MPM indication section<br>• Added use with amivantamab and carboplatin in first-line treatment of locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations<br>• Added use with amivantamab and carboplatin for locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations whose disease has progressed on or after treatment with an EGFR tyrosine kinase inhibitor<br>• Updated references |

# LEGAL AND COMPLIANCE

## Guideline Approval

### *Committee*

**Reviewed / Approved by Evolent Specialty Services Clinical Guideline Review Committee**

## Disclaimer

*Evolent Clinical Guidelines do not constitute medical advice. Treating health care professionals are solely responsible for diagnosis, treatment, and medical advice. Evolent uses Clinical Guidelines in accordance with its contractual obligations to provide utilization management. Coverage for services varies for individual members according to the terms of their health care coverage or government program. Individual members’ health care coverage may not utilize some Evolent Clinical Guidelines. Evolent clinical guidelines*

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