# Pemetrexed:
## Alimta®; Pemfexy™; Pemetrexed Ψ
## (Intravenous)

**-E-**

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## I. Length of Authorization [15,26,28-30]

Coverage will be provided for 6 months and may be renewed, unless otherwise specified.

- Thymomas: Coverage will be provided for six 21-day cycles and may not be renewed.
- MPM: Coverage will be provided for six 21-day cycles and may not be renewed when used in combination with platinum therapy and bevacizumab.

## II. Dosing Limits

**A. Quantity Limit (max daily dose) [NDC Unit]:**

- Alimta 100 mg powder for injection in a single-use vial: 4 vials every 21 days
- Alimta 500 mg powder for injection in a single-use vial: 4 vials every 21 days
- Pemfexy 500 mg solution for injection in a multi-dose vial: 4 vials every 21 days
- Pemetrexed 750 mg powder for injection: 2 vials every 21 days
- Pemetrexed 1000 mg powder for injection: 2 vials every 21 days
- Pemetrexed 100 mg/4 mL solution for injection: 4 vials every 21 days
- Pemetrexed 500 mg/20 mL solution for injection: 4 vials every 21 days
- Pemetrexed 1000 mg/40 mL solution for injection: 2 vials every 21 days

**B. Max Units (per dose and over time) [HCPCS Unit]:**

- Ovarian Cancer: 230 billable units every 21 days
- All other indications: 130 billable units every 21 days

## III. Initial Approval Criteria [1,2]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age; AND

**Malignant Pleural* Mesothelioma (MPM) † ‡ Φ** [1-6,10,26,31,79e,80e]

- Used as induction therapy; **AND**
  - Used in combination with cisplatin or carboplatin (if cisplatin ineligible) in patients with clinical stage I-IIIA disease and epithelioid histology; **OR**
- Used as first-line therapy; **AND**
  - Used in combination with bevacizumab AND cisplatin or carboplatin (if cisplatin ineligible) for unresectable disease; **OR**
  - Used in combination with cisplatin or carboplatin (if cisplatin ineligible); **AND**
    - Disease is unresectable or patient has resected disease without prior induction chemotherapy; **OR**
- Used as subsequent therapy; **AND**
  - Used as a single agent OR in combination with cisplatin or carboplatin (if cisplatin ineligible), with or without bevacizumab; **AND**
    - Immunotherapy was administered as first-line treatment; **OR**
    - Used as a rechallenge if a pemetrexed-based treatment was administered first-line with a good response

**Non-Squamous Non-Small Cell Lung Cancer (NS-NSCLC) † ‡** [1-3,7-9,11,12,28,30,50e,51e,54e,56e-58e,81e-83e]

- Used in combination with carboplatin or cisplatin; **OR**
- Used in combination with bevacizumab, pembrolizumab, cemiplimab, or durvalumab for continuation maintenance therapy if previously used first-line and patient achieved a tumor response or stable disease following initial therapy; **OR**
- Used in combination with cisplatin and nivolumab as neoadjuvant therapy for resectable (tumors ≥ 4 cm or node positive) disease; **OR**
- Used in combination with bevacizumab and either cisplatin or carboplatin; **AND**
  - Use of pemetrexed will be restricted to patients with a contraindication or intolerance to one of the following:
    - Bevacizumab/carboplatin/paclitaxel
    - Generically available regimen (e.g., carboplatin/docetaxel, etc. [*see NCCN Non-Small Cell Lung* Cancer *guidelines for complete list of alternative regimens*]); **OR**
- Used in combination with one of the following:
  - Pembrolizumab and either cisplatin or carboplatin
  - Cemiplimab and either cisplatin or carboplatin
  - Tremelimumab, durvalumab, and either cisplatin or carboplatin; **AND**

PD-L1 ≥50% (first-line therapy):

- Use of pemetrexed will be restricted to patients with a contraindication or intolerance to cemiplimab; **OR**

- Used in combination with nivolumab, ipilimumab, and either cisplatin or carboplatin; **AND**

PD-L1 ≥50% (first-line therapy):

- Use of pemetrexed will be restricted to patients with a contraindication or intolerance to cemiplimab; **OR**

All other treatment settings:

- Use of pemetrexed will be restricted to patients with a contraindication or intolerance to one of the following:
  - Pembrolizumab/carboplatin (or cisplatin)/pemetrexed
  - Cemiplimab/platinum-based chemotherapy
  - Tremelimumab/durvalumab/platinum-based chemotherapy; **OR**

- Used as a single agent; **AND**
  - Patient has recurrent, advanced, or metastatic disease (excluding locoregional recurrence or symptomatic local disease without evidence of disseminated disease) or mediastinal lymph node recurrence with prior radiation therapy; **AND**
    - Used as one of the following:
      - First-line therapy for tumors that are negative for actionable molecular biomarkers*****
      - First-line therapy for EGFR exon 20 mutation, KRAS G12C mutation, BRAF V600E-mutation, NTRK1/2/3 gene fusion, MET exon-14 skipping mutation, RET rearrangement positive tumors, or ERBB2 (HER2) mutation positive tumors
      - Subsequent therapy; **AND**

First-line therapy:

- Use of pemetrexed will be restricted to patients with a contraindication or intolerance to a generically available agent/regimen (e.g., gemcitabine, carboplatin/docetaxel, etc. [*see NCCN Non-Small Cell Lung Cancer guidelines for complete list of alternative agents/regimens*]); **OR**

    - Used as continuation or switch maintenance therapy in patients who have achieved a tumor response or stable disease following initial therapy

****** Note: Actionable molecular genomic biomarkers include EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET exon 14 skipping mutation, RET rearrangement, and ERBB2 (HER2). If there is insufficient tissue to allow testing for all of EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, and ERBB2 (HER2), 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.*

**Thymomas ‡** [3,14,15,25,68e]

- Used as a single agent; **AND**
- Used as second-line therapy for unresectable or metastatic disease; **AND**
- Use of pemetrexed will be restricted to patients with a contraindication or intolerance to a generically available agent/regimen (e.g., gemcitabine/capecitabine, etc. [*see NCCN Thymomas and Thymic Carcinomas guideline for complete list of alternative regimens*])

**Ovarian Cancer (including Fallopian Tube and Primary Peritoneal Cancer) ‡** [3,13,24,74e,75e]

- Used as a single agent; **AND**
  - Patient has recurrent or persistent Grade 1 Endometrioid Carcinoma, Carcinosarcoma (Malignant Mixed Müllerian Tumors), Mucinous Carcinoma of the Ovary, Epithelial Ovarian/Fallopian Tube/Primary Peritoneal Cancer, or Clear Cell Carcinoma of the Ovary; **AND**
    - Patient is not experiencing an immediate biochemical relapse (i.e., rising CA-125 without radiographic evidence of disease); **AND**
    - Patient has platinum-resistant disease; **AND**
    - Patient must demonstrate an inadequate response to a generically available agent (e.g., docetaxel, etoposide, etc.), unless there is a contraindication or intolerance, prior to approval of pemetrexed (*see NCCN Ovarian Cancer guideline for complete list of alternative agents*); **OR**
  - Patient has recurrent Low-Grade Serous Carcinoma; **AND**
    - Patient has platinum-resistant disease; **AND**
    - Patient must demonstrate an inadequate response to a generically available agent (e.g., docetaxel, etoposide, etc.), unless there is a contraindication or intolerance, prior to approval of pemetrexed (*see NCCN Ovarian Cancer guideline for complete list of alternative agents*)

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**Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.**

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); Φ Orphan Drug

| § Genomic Aberration/Mutational Driver Targeted Therapies (Note: *not all inclusive, refer to guidelines for appropriate use*) | | | | |
|---|---|---|---|---|
| Sensitizing *EGFR* mutation-positive tumors | *ALK* rearrangement-positive tumors | *ROS1* rearrangement-positive tumors | *BRAF* V600E-mutation positive tumors | *NTRK1/2/3* gene fusion positive tumors |
| – Afatinib<br>– Erlotinib<br>– Dacomitinib<br>– Gefitinib<br>– Osimertinib<br>– Amivantamab *(exon-20 insertion)*<br>– Mobocertinib *(exon-20 insertion)* | – Alectinib<br>– Brigatinib<br>– Ceritinib<br>– Crizotinib<br>– Lorlatinib | – Ceritinib<br>– Crizotinib<br>– Entrectinib<br>– Lorlatinib | – Dabrafenib ± trametinib<br>– Vemurafenib | – Larotrectinib<br>– Entrectinib |
| PD-L1 tumor expression ≥ 1% | *MET* exon-14 skipping mutations | *RET* rearrangement-positive tumors | *KRAS G12C* mutation positive tumors | *ERBB2 (HER2)* mutation positive tumors |
| – Pembrolizumab<br>– Atezolizumab<br>– Nivolumab + ipilimumab<br>– Cemiplimab<br>– Tremelimumab + durvalumab | – Capmatinib<br>– Crizotinib<br>– Tepotinib | – Selpercatinib<br>– Cabozantinib<br>– Pralsetinib | – Sotorasib<br>– Adagrasib | – Fam-trastuzumab deruxtecan-nxki<br>– Ado-trastuzumab emtansine |

## IV. Renewal Criteria [1,2]

Coverage may be renewed based upon the following criteria:

- Patient continues to meet the indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: myelosuppression (e.g., neutropenia, febrile neutropenia, thrombocytopenia, anemia), renal toxicity (CrCl < 45 mL/min), bullous and exfoliative skin toxicity (e.g., Stevens-Johnson Syndrome/Toxic epidermal necrolysis), interstitial pneumonitis, radiation recall, etc.; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**

**MPM** [26,29]

- May not be renewed when used in combination with platinum therapy and bevacizumab

**Thymomas** [15]

- May not be renewed

## V. Dosage/Administration [1,2,13,15,16,26,28-32]

| Indication | Dose |
|---|---|
| Non-Squamous NSCLC | Administer up to 500 mg/m$^2$ intravenously every 21 days |
| MPM | Administer 500 mg/m$^2$ intravenously every 21 days |

| | |
|---|---|
| | – For 6 cycles only when used in combination with platinum therapy and bevacizumab<br>– All others until disease progression or unacceptable toxicity |
| Ovarian Cancer | Administer 900 mg/m$^2$ intravenously every 21 days, until disease progression or unacceptable toxicity |
| Thymomas | Administer 500 mg/m$^2$ intravenously every 21 days for a maximum of 6 cycles in absence of disease progression or unacceptable toxicity |
| • Supplement with oral folic acid and intramuscular vitamin $B_{12}$.<br>• Avoid administration of ibuprofen for 2 days before, the day of, and 2 days following administration in patients with CrCl <80 mL/min.<br>• Do not dose in patients with CrCl <45 mL/min. | |

## VI. Billing Code/Availability Information

| Product Formulation | Drug | Manufacturer | Type | HCPCS Code | NDC |
|---|---|---|---|---|---|
| Pemetrexed Disodium Lyophilisate for injection | Alimta 100 mg powder for inj. SDV *<br>Alimta 500 mg powder for inj. SDV * | Lilly | Brand | J9305 | 00002-7640-xx<br>00002-7623-xx |
| | Pemetrexed 100 mg powder for inj. SDV Ψ<br>Pemetrexed 500 mg powder for inj. SDV Ψ<br>Pemetrexed 1000 mg powder for inj. SDV Ψ | Hospira | Brand | J9294 | 00409-1060-xx<br>00409-1061-xx<br>00409-1062-xx |
| | Pemetrexed 750 mg powder for inj. SDV *<br>Pemetrexed 1000 mg powder for inj. SDV * | N/A | Generic | J9305 | N/A |
| | Pemetrexed 100 mg powder for inj. SDV Ψ<br>Pemetrexed 500 mg powder for inj. SDV Ψ<br>Pemetrexed 750 mg powder for inj. SDV Ψ<br>Pemetrexed 1000 mg powder for inj. SDV Ψ | BluePoint | Brand | J9322 | 68001-0543-xx<br>68001-0544-xx<br>68001-0545-xx<br>68001-0546-xx |
| Pemetrexed Disodium Solution for injection | Pemetrexed 100 mg/4 mL inj. SDV Ψ | Sandoz | Brand | J9297 | 00781-3518-xx |
| | | Accord | Brand | J9296 | 16729-0522-xx |
| | | Hospira | Brand | J9294 | 00409-1045-xx |
| | Pemetrexed 500 mg/20 mL inj. SDV Ψ | Sandoz | Brand | J9297 | 00781-3519-xx |
| | | Accord | Brand | J9296 | 16729-0522-xx |
| | | Hospira | Brand | J9294 | 00409-2188-xx |
| | Pemetrexed 1000 mg/40 mL inj. SDV Ψ | Sandoz | Brand | J9321 | 00781-3520-xx |
| | | Accord | Brand | J9296 | 16729-0522-xx |
| | | Hospira | Brand | J9294 | 00409-3532-xx |
| Pemetrexed Solution for injection | Pemfexy 500 mg/20 mL inj. MDV | Eagle | Brand | J9304 | 42367-0531-xx |
| | Pemetrexed 100 mg/4mL inj. SDV Ψ | Teva | Brand | J9314 | 00480-4516-xx |
| | Pemetrexed 500 mg/20 mL inj. SDV Ψ | Teva | Brand | J9314 | 00480-4514-xx |
| | Pemetrexed 1000 mg/40 mL inj. SDV Ψ | Teva | Brand | J9314 | 00480-4515-xx |
| Pemetrexed Ditromethamine for injection | Pemetrexed 100 mg powder for inj. SDV Ψ | Hospira | Brand | J9323 | 00409-1060-xx |
| | Pemetrexed 500 mg powder for inj. SDV Ψ | Hospira | Brand | J9323 | 00409-1061-xx |
| | Pemetrexed 1000 mg powder for inj. SDV Ψ | Hospira | Brand | J9323 | 00409-1062-xx |

***Multiple manufacturers produce ANDA generics***

**Ψ** *Designated products approved by the FDA as a 505(b)(2) NDA of the innovator product. These products are not rated as therapeutically equivalent to their reference listed drug in the Food and Drug Administration's (FDA) Orange Book and are therefore considered single source products based on the statutory definition of "single source drug" in section 1847A(c)(6) of the Act. For a complete list of all approved 505(b)(2) NDA products please reference the latest edition of the Orange Book: [Approved Drug Products with Therapeutic Equivalence Evaluations | Orange Book | FDA]*

**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**
**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**
**J9323 - Injection, pemetrexed (hospira) not therapeutically equivalent to J9305, 10 mg *(Effective 07/01/2023)***
**J9321 - Injection, pemetrexed (sandoz) not therapeutically equivalent to J9305, 10 mg *(Effective 07/01/2023)***
**J9322 - Injection, pemetrexed (bluepoint) not therapeutically equivalent to J9305, 10 mg *(Effective 07/01/2023)***

## VII. References (STANDARD)


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## Appendix 1 – Covered Diagnosis Codes

| ICD-10 | ICD-10 Description |
|---|---|
| C33 | Malignant neoplasm of trachea |
| C34.00 | Malignant neoplasm of unspecified main bronchus |
| C34.01 | Malignant neoplasm of right main bronchus |
| C34.02 | Malignant neoplasm of left main bronchus |

| ICD-10 | ICD-10 Description |
|---|---|
| C34.10 | Malignant neoplasm of upper lobe, unspecified bronchus or lung |
| C34.11 | Malignant neoplasm of upper lobe, right bronchus or lung |
| C34.12 | Malignant neoplasm of upper lobe, left bronchus or lung |
| C34.2 | Malignant neoplasm of middle lobe, bronchus or lung |
| C34.30 | Malignant neoplasm of lower lobe, unspecified bronchus or lung |
| C34.31 | Malignant neoplasm of lower lobe, right bronchus or lung |
| C34.32 | Malignant neoplasm of lower lobe, left bronchus or lung |
| C34.80 | Malignant neoplasm of overlapping sites of unspecified bronchus or lung |
| C34.81 | Malignant neoplasm of overlapping sites of right bronchus and lung |
| C34.82 | Malignant neoplasm of overlapping sites of left bronchus and lung |
| C34.90 | Malignant neoplasm of unspecified part of unspecified bronchus or lung |
| C34.91 | Malignant neoplasm of unspecified part of right bronchus or lung |
| C34.92 | Malignant neoplasm of unspecified part of left bronchus or lung |
| C37 | Malignant neoplasm of thymus |
| C45.0 | Mesothelioma of pleura |
| C48.1 | Malignant neoplasm of specified parts of peritoneum |
| C48.2 | Malignant neoplasm of peritoneum, unspecified |
| C48.8 | Malignant neoplasm of overlapping sites of retroperitoneum and peritoneum |
| C56.1 | Malignant neoplasm of right ovary |
| C56.2 | Malignant neoplasm of left ovary |
| C56.3 | Malignant neoplasm of bilateral ovaries |
| C56.9 | Malignant neoplasm of unspecified ovary |
| C57.00 | Malignant neoplasm of unspecified fallopian tube |
| C57.01 | Malignant neoplasm of right fallopian tube |
| C57.02 | Malignant neoplasm of left fallopian tube |
| C57.10 | Malignant neoplasm of unspecified broad ligament |
| C57.11 | Malignant neoplasm of right broad ligament |
| C57.12 | Malignant neoplasm of left broad ligament |
| C57.20 | Malignant neoplasm of unspecified round ligament |
| C57.21 | Malignant neoplasm of right round ligament |
| C57.22 | Malignant neoplasm of left round ligament |
| C57.3 | Malignant neoplasm of parametrium |
| C57.4 | Malignant neoplasm of uterine adnexa, unspecified |
| C57.7 | Malignant neoplasm of other specified female genital organs |

| ICD-10 | ICD-10 Description |
|---|---|
| C57.8 | Malignant neoplasm of overlapping sites of female genital organs |
| C57.9 | Malignant neoplasm of female genital organ, unspecified |
| D15.0 | Benign neoplasm of thymus |
| D38.4 | Neoplasm of uncertain behavior of thymus |
| Z85.118 | Personal history of other malignant neoplasm of bronchus and lung |
| Z85.238 | Personal history of other malignant neoplasm of thymus |
| Z85.43 | Personal history of malignant neoplasm of ovary |

## Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

| Medicare Part B Administrative Contractor (MAC) Jurisdictions | | |
|---|---|---|
| **Jurisdiction** | **Applicable State/US Territory** | **Contractor** |
| E (1) | CA, HI, NV, AS, GU, CNMI | Noridian Healthcare Solutions, LLC |
| F (2 & 3) | AK, WA, OR, ID, ND, SD, MT, WY, UT, | Noridian Healthcare Solutions, LLC |
| 5 | KS, NE, IA, MO | Wisconsin Physicians Service Insurance Corp |
| 6 | MN, WI, IL | National Government Services, Inc. (NGS) |
| H (4 & 7) | LA, AR, MS, TX, OK, CO, NM | Novitas Solutions, Inc. |
| 8 | MI, IN | Wisconsin Physicians Service Insurance Corp |
| N (9) | FL, PR, VI | First Coast Service Options, Inc. |
| J (10) | TN, GA, AL | Palmetto GBA, LLC |
| M (11) | NC, SC, WV, VA (excluding below) | Palmetto GBA, LLC |
| L (12) | DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA) | Novitas Solutions, Inc. |
| K (13 & 14) | NY, CT, MA, RI, VT, ME, NH | National Government Services, Inc. (NGS) |
| 15 | KY, OH | CGS Administrators, LLC |