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

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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/Thymic Carcinoma: Coverage will be provided for six 21-day cycles and may not be renewed.
- MPeM and MPM: Coverage will be provided for six 21-day cycles and may not be renewed when used in combination with platinum therapy and bevacizumab.
- NSCLC: Coverage will be provided for four 21-day cycles and may not be renewed when used for adjuvant therapy OR neoadjuvant therapy when used in combination with carboplatin and cisplatin.
- NSCLC: Coverage will be provided for three 21-day cycles and may not be renewed when used for neoadjuvant therapy in combination with nivolumab and cisplatin.

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 disodium 750mg powder for injection: 2 vials every 21 days
- Pemetrexed disodium 1000mg powder for injection: 2 vials every 21 days
- Pemetrexed disodium 100mg/4 mL solution for injection: 4 vials every 21 days
- Pemetrexed disodium 500mg/20 mL solution for injection: 4 vials every 21 days
- Pemetrexed disodium 1000mg/40 mL solution for injection: 2 vials every 21 days

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

- CNS Lymphoma and 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**

Primary Central Nervous System (CNS) Lymphoma ‡ [3,16,27]

- Used as single-agent induction therapy in patients unsuitable for or intolerant to high-dose methotrexate (MTX); **OR**
- Used as single agent therapy for relapsed or refractory disease; **AND**
  - Patient received prior whole brain radiation therapy (RT); **OR**
  - Patient received a prior high-dose MTX-based regimen without prior RT; **OR**
  - Used in combination with whole brain RT or involved field RT in patients who received a prior high-dose MTX-based regimen without prior RT with either no response or short response (<12 month duration) to prior regimen; **OR**
  - Patient received prior high-dose chemotherapy with stem cell rescue

Malignant Peritoneal Mesothelioma* (MPeM) ‡ [3,29]

- Used as first-line therapy; **AND**
  - Used in combination with bevacizumab AND cisplatin or carboplatin (if cisplatin ineligible); **AND**
    - Patient has unresectable diffuse disease; **OR**
    - Patient has unresectable recurrent benign multicystic or well-differentiated papillary disease; **OR**
  - Used as a single agent OR in combination with cisplatin or carboplatin (if cisplatin ineligible); **AND**
    - Used as adjuvant treatment of diffuse disease in patients with surgical/pathologic high-risk features** who have not received neoadjuvant therapy; **OR**
    - Patient has diffuse disease; **OR**
    - Patient has recurrent benign multicystic or well-differentiated papillary disease; **OR**
- Used as subsequent therapy; **AND**
  - Immunotherapy was administered as first-line treatment; **AND**
    - Used in combination with cisplatin with or without bevacizumab; **OR**
    - Used in combination with carboplatin (if cisplatin ineligible) with or without bevacizumab; **OR**

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- Used as a single agent; **AND**
  - Pemetrexed was not administered first-line; **OR**
  - Used as rechallenge if pemetrexed was administered first-line with a good sustained response at the time initial chemotherapy was interrupted

** Note: May also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma.*

*** High-risk features include Ki-67 >9%, nodal metastasis, high tumor burden (Peritoneal Cancer Index [PCI] >17), completeness of cytoreduction (CC) score >1, biphasic disease, or bicavitary disease*

Malignant Pleural* Mesothelioma (MPM) † Φ [1-6,10,26]

- Used as induction therapy; **AND**
  - Used in combination with cisplatin or carboplatin (if cisplatin ineligible); **AND**
  - Patient has stage I-IIIA disease with epithelioid histology; **OR**
- Used as first-line therapy; **AND**
  - Used in combination with bevacizumab AND cisplatin or carboplatin (if cisplatin ineligible); **AND**
    - Patient has unresectable stage I-IIIA disease with epithelioid histology and has not previously been treated with induction chemotherapy; **OR**
    - Patient has stage IIIB or IV disease, sarcomatoid or biphasic histology, or medically inoperable tumors; **OR**
  - Used as a single agent OR in combination with cisplatin or carboplatin (if cisplatin ineligible); **AND**
    - Patient has unresectable stage I-IIIA disease with epithelioid histology and has not previously been treated with induction chemotherapy; **OR**
    - Patient has resected stage I-IIIA disease with epithelioid histology and has not previously been treated with induction chemotherapy; **OR**
    - Patient has stage IIIB or IV disease, sarcomatoid or biphasic histology, or medically inoperable tumors; **OR**
- Used as subsequent therapy; **AND**
  - Immunotherapy was administered as first-line treatment; **AND**
    - Used in combination with cisplatin with or without bevacizumab; **OR**
    - Used in combination with carboplatin (if cisplatin ineligible) with or without bevacizumab; **OR**
  - Used as a single agent; **AND**
    - Pemetrexed was not administered first-line; **OR**
    - Used as rechallenge if pemetrexed was administered first-line with a good sustained response at the time initial chemotherapy was interrupted

** Note: May also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma.*

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Non-Squamous Non-Small Cell Lung Cancer (NS-NSCLC) † [1-3,7-9,11,12,28,30]

- Used as induction therapy; **AND**
  - Used in combination with carboplatin or cisplatin; **OR**
  - Used in combination with cisplatin and nivolumab for patients likely to receive adjuvant chemotherapy (i.e., resectable [tumors ≥4 cm or node positive] disease); **OR**
- Used as initial treatment as definitive concurrent chemoradiation; **AND**
  - Used in combination with carboplatin or cisplatin for unresectable, advanced, or metastatic disease; **OR**
- Used as neoadjuvant therapy; **AND**
  - Used in combination with carboplatin or cisplatin; **OR**
  - Used in combination with nivolumab and cisplatin for resectable (tumors ≥ 4 cm or node positive) disease; **OR**
- Used as adjuvant therapy; **AND**
  - Used in combination with carboplatin or cisplatin; **OR**
  - Used as concurrent or sequential chemoradiation in combination with carboplatin or cisplatin for locally advanced disease; **OR**
- Used for locoregional recurrence or symptomatic local disease; **AND**
  - Used as concurrent chemoradiation (if radiation not previously given) in combination with carboplatin or cisplatin; **AND**
  - Patient has superior vena cava obstruction or mediastinal lymph nodal disease; **OR**
- Used for 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 first-line therapy; **AND**
    - Used for PD-L1 ≥1% tumors that have negative actionable molecular biomarkers*; **AND**
      - Used in combination with bevacizumab and either cisplatin or carboplatin in patients with PS 0-1 and contraindications¥ to PD-1 or PD-L1 inhibitors; **OR**
      - Used in combination with pembrolizumab and either carboplatin or cisplatin in patients with PS 0-2; **OR**
      - Used in combination with nivolumab, ipilimumab, and either carboplatin or cisplatin in patients with PS 0-2; **OR**
      - Used in combination with cisplatin in patients with PS 0-1 and contraindications¥ to PD-1 or PD-L1 inhibitors; **OR**
      - Used in combination with carboplatin in patients with PS 0-2 and contraindications¥ to PD-1 or PD-L1 inhibitors; **OR**
      - Used as a single agent in patients with PS 2; **OR**

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- Used for one of the following:
  - PD-L1 <1% and tumors that have negative actionable molecular markers *; **OR**
  - BRAF V600E-mutation, NTRK1/2/3 gene fusion, MET exon-14 skipping mutation, EGFR exon 20 mutation, KRAS G12C mutation, or RET rearrangement positive tumors; **AND**
  - Used as a single agent in patients with PS 2; **OR**
  - Used in combination with pembrolizumab and either carboplatin or cisplatin in patients with PS 0-1; **OR**
  - Used in combination with cisplatin in patients with PS 0-1 and contraindications¥ to PD-1 or PD-L1 inhibitors; **OR**
  - Used in combination with carboplatin in patients with PS 0-2 and contraindications¥ to PD-1 or PD-L1 inhibitors; **OR**
  - Used in combination with nivolumab, ipilimumab, and either carboplatin or cisplatin in patients with PS 0-1; **OR**
  - Used in combination with bevacizumab and either cisplatin or carboplatin in patients with PS 0-1 and contraindications¥ to PD-1 or PD-L1 inhibitors; **OR**

- Used as subsequent therapy; **AND**
  - Used as a single-agent (if not previously given) in patients with a PS 0-2; **AND**
    - Used for first progression after initial systemic therapy; **OR**
  - Used for one of the following:
    - EGFR exon 19 deletion or L858R; EGFR S768I, L861Q, and/or G719X; ALK rearrangement; or ROS1 rearrangement positive tumors and prior targeted therapy§ for those aberrations; **OR**
    - BRAF V600E-mutation, NTRK1/2/3 gene fusion, MET exon-14 skipping mutation, or RET rearrangement positive tumors; **OR**
    - PD-L1 ≥ 1% tumors that have negative actionable molecular biomarkers* with prior PD-1/PD-L1 inhibitor therapy but no prior platinum doublet chemotherapy; **AND**
    - Used in combination with pembrolizumab and either carboplatin or cisplatin in patients with PS 0-1; **OR**
    - Used in combination with cisplatin in patients with PS 0-1 and contraindications¥ to PD-1 or PD-L1 inhibitors; **OR**
    - Used in combination with carboplatin in patients with PS 0-2 and contraindications¥ to PD-1 or PD-L1 inhibitors; **OR**
    - Used in combination with nivolumab, ipilimumab, and either carboplatin or cisplatin in patients with PS 0-1; **OR**

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        - Used in combination with bevacizumab and either cisplatin or carboplatin in patients with PS 0-1 and contraindications¥ to PD-1 or PD-L1 inhibitors; **OR**
    - Used as maintenance therapy in patients who have achieved tumor response or stable disease following initial therapy; **AND**
        - Used as a single agent for continuation maintenance therapy; **OR**
        - Used as a single agent for switch maintenance therapy; **OR**
        - Used for continuation maintenance therapy in combination with bevacizumab following a first-line bevacizumab/pemetrexed/platinum chemotherapy regimen; **OR**
        - Used for continuation maintenance therapy in combination with pembrolizumab following a first-line pembrolizumab/pemetrexed and either carboplatin or cisplatin regimen

** Note: Actionable molecular genomic biomarkers include EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET exon 14 skipping mutation, and RET rearrangement. If there is insufficient tissue to allow testing for all of EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, and RET, 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.*
¥ Note: Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents, or presence of an oncogene (e.g., EGFR exon 19 deletion or L858R, ALK rearrangements), which would predict lack of benefit.

Thymomas/Thymic Carcinoma ‡ [3,14,15,25]

- Used as a single agent; **AND**
    - Used as first line therapy or postoperative treatment in patients who are unable to tolerate first-line combination regimens; **OR**
    - Used as second-line therapy for unresectable or metastatic disease

Ovarian Cancer (Epithelial Ovarian/Fallopian Tube/Primary Peritoneal Cancer) ‡ [3,13,24]

- Patient has recurrent or persistent disease; **AND**
    - Patient is not experiencing an immediate biochemical relapse (i.e., rising CA-125 without radiographic evidence of disease); **AND**
        - Used as a single agent; **AND**
            - Patient has platinum-resistant disease; **AND**
                - Used for progression on primary, maintenance, or recurrence therapy; **OR**
                - Used for stable or persistent disease if not currently on maintenance therapy; **OR**
                - Used for relapsed disease <6 months following complete remission from prior chemotherapy; **OR**

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- Patient has platinum-sensitive disease; **AND**
  - Used for radiographic and/or clinical relapse ≥6 months after complete remission from prior chemotherapy; **OR**

- Patient has recurrent low-grade serous carcinoma; **AND**
  - Used as a single agent for platinum-sensitive or platinum-resistant disease

† 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**	***NTRK* 1/2/3 gene fusion positive tumors**
– Afatinib – Erlotinib – Dacomitinib – Gefitinib – Osimertinib – Amivantamab *(exon-20 insertion)* – Mobocertinib *(exon-20 insertion)*	– Alectinib – Brigatinib – Ceritinib – Crizotinib – Lorlatinib	– Ceritinib – Crizotinib – Entrectinib – Lorlatinib	– Dabrafenib ± trametinib – Vemurafenib	– Larotrectinib – Entrectinib
PD-L1 tumor expression ≥ 1%	**PD-L1 tumor expression ≥ 50%**	***MET* exon-14 skipping mutations**	***RET* rearrangement-positive tumors**	***KRAS G12C* mutation positive tumors**
– Pembrolizumab – Atezolizumab – Nivolumab + ipilimumab	– Pembrolizumab – Atezolizumab – Nivolumab + ipilimumab – Cemiplimab	– Capmatinib – Crizotinib – Tepotinib	– Selpercatinib – Cabozantinib – Pralsetinib	– Sotorasib

IV. Renewal Criteria [1,2]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet 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**

Continuation of Maintenance Therapy for Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

- *Refer to Section III for criteria*

Non-Squamous Non-Small Cell Lung Cancer (NSCLC) (neoadjuvant or adjuvant therapy) [28]

- May not be renewed

MPeM and MPM [26,29]

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

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Thymomas/Thymic Carcinoma [15]

- May not be renewed

V. Dosage/Administration [1,2,13,15,16,26,28-30]

Indication	Dose
Non-Squamous NSCLC	Administer 500 mg/m^2 intravenously every 21 days – Adjuvant therapy: treatment is given for 4 cycles only – Neoadjuvant therapy in combination with carboplatin or cisplatin: treatment is given for 4 cycles only – Neoadjuvant therapy in combination with nivolumab and cisplatin: treatment is given for 3 cycles only – All others until disease progression or unacceptable toxicity
MPM, MPeM	Administer 500 mg/m^2 intravenously every 21 days – For 6 cycles only when used in combination with platinum therapy and bevacizumab – All others until disease progression or unacceptable toxicity
Primary CNS Lymphoma, Ovarian Cancer	Administer 900 mg/m^2 intravenously every 21 days, until disease progression or unacceptable toxicity
Thymomas/Thymic Carcinoma	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} • Avoid administration of ibuprofen for 2 days before, the day of, and 2 days following administration in patients with CrCl <80 mL/min. • Do not dose in patients with CrCl <45 mL/min	

VI. Billing Code/Availability Information

HCPCS Code:

- J9305 – Injection, pemetrexed, not otherwise specified, 10 mg; 1 billable unit = 10mg
- J9304 – Injection, pemetrexed (pemfexy), 10 mg; 1 billable unit = 10mg *(Pemfexy Only)*

NDC:

- Alimta 100 mg powder for injection; single-dose vial: 00002-7640-xx *
- Alimta 500 mg powder for injection; single-dose vial: 00002-7623-xx *
- Pemfexy 500 mg/20 mL solution for injection, multi-dose vial: 42367-0531-xx
- Pemetrexed disodium 750mg powder for injection: *Available only as a multi-sourced generic*
- Pemetrexed disodium 1000mg powder for injection: *Available only as a multi-sourced generic*

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- Pemetrexed disodium 100mg/4 mL solution for injection: *Approved by the FDA as a 505(b)(2) NDA of the innovator product*
- Pemetrexed disodium 500mg/20 mL solution for injection: *Approved by the FDA as a 505(b)(2) NDA of the innovator product*
- Pemetrexed disodium 1000mg/40 mL solution for injection: *Approved by the FDA as a 505(b)(2) NDA of the innovator product*

**Available generically*

VII. References

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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
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
C45.1	Mesothelioma of peritoneum
C45.2	Mesothelioma of pericardium
C45.7	Mesothelioma of other sites
C45.9	Mesothelioma, unspecified
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

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ICD-10	ICD-10 Description
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
C57.8	Malignant neoplasm of overlapping sites of female genital organs
C57.9	Malignant neoplasm of female genital organ, unspecified
C83.30	Diffuse large B-cell lymphoma unspecified site
C83.39	Diffuse large B-cell lymphoma extranodal and solid organ sites
C83.80	Other non-follicular lymphoma, unspecified site
C83.89	Other non-follicular lymphoma, extranodal and solid organ sites
C85.89	Other specified types of non-Hodgkin lymphoma, extranodal and solid organ sites
C85.99	Non-Hodgkin's lymphoma extranodal and solid organ sites
D15.0	Benign neoplasm of thymus
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
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

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Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
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

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