Pemetrexed:
Alimta®; Pemfexy™
(Intravenous)

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I. Length of Authorization [15,26,28,29]

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.
- NSCLC: Coverage will be provided for four 21-day cycles and may not be renewed when used for neoadjuvant or adjuvant therapy.

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

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 [1-6,10,26,79e,80e]

- 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 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**
  - 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:** Pericardial and tunica vaginalis testis mesothelioma will be evaluated on a case-by-case basis.*

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 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; **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 (*see NCCN Non-Small Cell Lung Cancer guidelines for complete list of alternative regimens*); **OR**

      - Used in combination with pembrolizumab and either carboplatin or cisplatin in patients with PS 0-2; **AND**

        PD-L1 ≥50%:

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

      - Used in combination with nivolumab, ipilimumab, and either carboplatin or cisplatin in patients with PS 0-2; **AND**

        PD-L1 ≥50%:

        – Use of pemetrexed will be restricted to patients with a contraindication or intolerance to cemiplimab

        PD-L1 ≥1%–49%:

        – Use of pemetrexed will be restricted to patients with a contraindication or intolerance to pembrolizumab/carboplatin (or cisplatin)/pemetrexed; **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; **AND**

        – 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 for one of the following:
  - PD-L1 <1% tumors that have negative actionable molecular markers*****
  - 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; **AND**

  - 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 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; **AND**

  - Use of pemetrexed will be restricted to patients with a contraindication or intolerance to pembrolizumab/carboplatin (or cisplatin)/pemetrexed; **OR**
- Used in combination with bevacizumab and either carboplatin or cisplatin in patients with PS 0-1 and contraindications**¥** to PD-1 or PD-L1 inhibitors; **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 (*see NCCN Non-Small Cell Lung* Cancer *guidelines for complete list of alternative regimens*); **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
    - BRAF V600E-mutation, NTRK1/2/3 gene fusion, MET exon-14 skipping mutation, or RET rearrangement positive tumors

- 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; **AND**

- Use of pemetrexed will be restricted to patients with a contraindication or intolerance to pembrolizumab/carboplatin (or cisplatin)/pemetrexed; **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; **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 (*see NCCN Non-Small Cell Lung Cancer guidelines for complete list of alternative regimens*); **OR**

o 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 following a first-line platinum chemotherapy regimen without pemetrexed; **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 ‡ [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 (Epithelial Ovarian/Fallopian Tube/Primary Peritoneal Cancer) ‡ [3,13,24,74e,75e]

- 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 one the following:
  - Progression on primary, maintenance, or recurrence therapy
  - Relapsed disease <6 months following complete remission from prior chemotherapy; **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*)

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 – Erlotinib – Dacomitinib – Gefitinib	– Alectinib – Brigatinib – Ceritinib – Crizotinib	– Ceritinib – Crizotinib – Entrectinib – Lorlatinib	– Dabrafenib ± trametinib – Vemurafenib	– Larotrectinib – Entrectinib

– Osimertinib – Amivantamab *(exon-20 insertion)* – Mobocertinib *(exon-20 insertion)*	– Lorlatinib			
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

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 [1,2,13,15,16,26,28,29]

Indication	Dose
Non-Squamous NSCLC	Administer 500 mg/m^2 intravenously every 21 days, until disease progression or unacceptable toxicity* *(*Note: When used for neoadjuvant or adjuvant therapy, treatment is given up to 4 cycles)*
MPM	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
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} • 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

NDC:

- Alimta 100 mg powder for injection; single-use vial: 00002-7640-xx
- Alimta 500 mg powder for injection; single-use vial: 00002-7623-xx
- Pemfexy 500 mg/20 mL solution for injection, multi-dose vial: 42367-0531-xx

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
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
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