Pemetrexed:
Alimta®; Pemfexy™; Pemetrexed Ψ
(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.

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]:

- Primary CNS Lymphoma, Cervical Cancer, and Ovarian Cancer: 230 billable units every 21 days
- Leptomeningeal Metastases from NSCLC: 5 billable units every 28 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**

Central Nervous System (CNS) Cancers‡ [3,16,27,33]

- Used as a single agent; **AND**
  - Patient has Primary Central Nervous System (CNS) Lymphoma; **AND**
    - Used as induction therapy in patients unsuitable for or intolerant to high-dose methotrexate (MTX); **OR**
    - Used for relapsed or refractory disease; **OR**
  - Patient has leptomeningeal metastases from EGFR mutation-positive non-small cell lung cancer; **AND**
    - Used as primary treatment in patients with good risk status (i.e., KPS ≥60, no major neurologic deficits, minimal systemic disease, and reasonable systemic treatment options if needed); **OR**
    - Used as maintenance treatment in patients with negative cerebrospinal fluid (CSF) cytology or in clinically stable patients with persistently positive CSF cytology

Cervical Cancer ‡ [3]

- Used as subsequent therapy for recurrent or metastatic disease; **AND**
- Patient has squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma; **AND**
- Used as a single agent

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

- Used as adjuvant therapy; **AND**
  - Patient has unicavitary disease with epithelioid histology; **AND**
  - Patient has surgical/pathologic high-risk features** and no neoadjuvant therapy was given; **AND**
  - Used as a single agent OR in combination with cisplatin or carboplatin (if cisplatin ineligible); **OR**
- Used as first-line therapy; **AND**
  - Used in combination with bevacizumab AND cisplatin or carboplatin (if cisplatin ineligible) for unresectable diffuse or recurrent disease; **OR**
  - Used as a single agent OR in combination with cisplatin or carboplatin (if cisplatin ineligible) for diffuse or recurrent disease; **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**

- Nivolumab and ipilimumab were administered as first-line treatment; **OR**
- Used as a rechallenge if a pemetrexed-based treatment was administered first-line with a good response

***** *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) 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 as a single agent OR 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**
    - Nivolumab and ipilimumab was administered as first-line treatment; **OR**
    - Used as a rechallenge if a pemetrexed-based treatment was administered first-line with a good response

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

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

- Used in combination with a carboplatin or cisplatin-containing regimen; **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 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 first-line therapy for tumors that are negative for actionable molecular biomarkers*; **OR**

- Used as 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, or ERBB2 (HER2) mutation positive tumors; **OR**
- Used as subsequent therapy; **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/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 (including Fallopian Tube and Primary Peritoneal Cancer) ‡ [3,13,24]

- 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); **OR**
  - Patient has recurrent Low-Grade Serous Carcinoma

† 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 – 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%	*MET* exon-14 skipping mutations	*RET* rearrangement-positive tumors	*KRAS G12C* mutation positive tumors	*ERBB2 (HER2)* mutation positive tumors

– Pembrolizumab – Atezolizumab – Nivolumab + ipilimumab – Cemiplimab – Tremelimumab + durvalumab	– Capmatinib – Crizotinib – Tepotinib	– Selpercatinib – Cabozantinib – Pralsetinib	– Sotorasib – Adagrasib	– Fam-trastuzumab deruxtecan-nxki – 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**

MPeM and MPM [26,29]

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

Thymomas/Thymic Carcinoma [15]

- May not be renewed

V. Dosage/Administration [1,2,10,13,15,16,26,28-33]

Indication	Dose
Non-Squamous NSCLC	Administer up to 500 mg/m^2 intravenously every 21 days
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
Ovarian Cancer, Cervical 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
CNS Cancers	Leptomeningeal metastases from EGFR mutation-positive non-small cell lung cancer Administer 50 mg intrathecally every 28 days, until disease progression or unacceptable toxicity

	Primary CNS Lymphoma Administer 900 mg/m2 intravenously every 21 days, until 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

Product Formulation	Drug	Manufacturer	Type	HCPCS Code	NDC
Pemetrexed Disodium Lyophilisate for injection	Alimta 100 mg powder for inj. SDV * Alimta 500 mg powder for inj. SDV *	Lilly	Brand	J9305	00002-7640-xx 00002-7623-xx
	Pemetrexed 100 mg powder for inj. SDV Ψ Pemetrexed 500 mg powder for inj. SDV Ψ Pemetrexed 1000 mg powder for inj. SDV Ψ	Hospira	Brand	J9294	00409-1060-xx 00409-1061-xx 00409-1062-xx
	Pemetrexed 750 mg powder for inj. SDV * Pemetrexed 1000 mg powder for inj. SDV *	N/A	Generic	J9305	N/A
	Pemetrexed 100 mg powder for inj. SDV Ψ Pemetrexed 500 mg powder for inj. SDV Ψ Pemetrexed 750 mg powder for inj. SDV Ψ Pemetrexed 1000 mg powder for inj. SDV Ψ	BluePoint	Brand	J9322	68001-0543-xx 68001-0544-xx 68001-0545-xx 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

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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

ICD-10	ICD-10 Description
C53.0	Malignant neoplasm of endocervix
C53.1	Malignant neoplasm of exocervix
C53.8	Malignant neoplasm of overlapping sites of cervix uteri
C53.9	Malignant neoplasm of cervix uteri, unspecified
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
C57.8	Malignant neoplasm of overlapping sites of female genital organs
C57.9	Malignant neoplasm of female genital organ, unspecified
C79.32	Secondary malignant neoplasm of cerebral meninges
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
D19.1	Benign neoplasm of mesothelial tissue of peritoneum
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

ICD-10	ICD-10 Description
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