Pemetrexed:
Alimta®; Pemfexy™; Pemrydi RTU™; Axtle™; Pemetrexed Ψ
(Intravenous)

-E-

Document Number: MODA-0489

Last Review Date: 10/03/2024
Date of Origin: 08/05/2019
Dates Reviewed: 08/2019, 10/2019, 01/2020, 04/2020, 07/2020, 10/2020, 01/2021, 05/2021, 07/2021, 10/2021, 02/2022, 04/2022, 07/2022, 10/2022, 01/2023, 04/2023, 08/2023, 10/2023, 01/2024, 04/2024, 07/2024, 10/2024

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 (6) 21-day cycles and may NOT be renewed.
- Mesothelioma (including PeM and PM) in combination with bevacizumab AND either cisplatin or carboplatin: Coverage will be provided for six (6) cycles and may NOT be renewed.

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 850 mg/34 mL solution for injection: 2 vials every 21 days
- Pemetrexed 1000 mg/40 mL solution for injection: 2 vials every 21 days
- Pemrydi RTU 100 mg/10 mL solution for injection: 4 vials every 21 days
- Pemrydi RTU 500 mg/50 mL solution for injection: 4 vials every 21 days
- Pemrydi RTU 1000 mg/100 mL solution for injection: 2 vials every 21 days

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

- Pemfexy (500 mg MDV):
  - Ovarian Cancer, Fallopian Tube, and Primary Peritoneal Cancer: 225 billable units every 21 days
  - Thymomas, Non-Squamous NSCLC, & Mesotheliomas: 125 billable units every 21 days

- Pemetrexed (all other manufacturers) (100 mg, 500 mg, 750 mg, 850 mg, and 1000 mg SDV):
  - Ovarian Cancer, Fallopian Tube, and Primary Peritoneal Cancer: 230 billable units every 21 days
  - Thymomas, Non-Squamous NSCLC, & Mesotheliomas: 130 billable units every 21 days

III. Initial Approval Criteria [1-3]

Coverage is provided in the following conditions:

- Patient must have a contraindication, intolerance, or failure to ALL alternative pemetrexed products prior to consideration of Pemfexy (J9304) and Pemrydi (J9324) and Axtle (J9292); **AND**

- Patient is at least 18 years of age; **AND**

Peritoneal Mesothelioma (PeM) ‡ [4,30]

- Used as adjuvant therapy; **AND**
  - Used in combination with cisplatin or carboplatin (if cisplatin ineligible); **AND**
    - Patient has unicavitary disease with epithelioid histology; **AND**
    - Patient has surgical/pathologic high-risk features****** and no neoadjuvant therapy was given; **OR**
- Used as first-line therapy; **AND**
  - Used in combination with cisplatin or carboplatin (if cisplatin ineligible), with or without bevacizumab; **AND**
    - Patient has biphasic/sarcomatoid histology or bicavitary disease; **OR**
    - Patient has unicavitary disease with epithelioid histology; **AND**
      - Patient is medically inoperable and/or complete cytoreduction is not achievable (including high-risk features******); **OR**
      - Patient has recurrent disease after prior cytoreductive surgery (CRS) + hyperthermic intraperitoneal (IP) chemotherapy (HIPEC) and no previous adjuvant systemic therapy was given; **OR**
- Used as subsequent therapy; **AND**
  - Used in combination with cisplatin or carboplatin (if cisplatin ineligible), with or without bevacizumab; **AND**
    - Immunotherapy (i.e., nivolumab/ipilimumab) was administered as first-line treatment; **OR**
    - Used as a rechallenge if pemetrexed-based treatment was administered first-line with good response

****** *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*

Pleural Mesothelioma (PM) † ‡ Φ [1-7,11,27,79e,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 either cisplatin or carboplatin (if cisplatin ineligible); **AND**
    - Patient has unresectable disease; **OR**
  - Used in combination with cisplatin or carboplatin (if cisplatin ineligible); **AND**
    - Disease is unresectable or patient is not a candidate for curative surgery; **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 (i.e., nivolumab/ipilimumab) was administered as first-line treatment; **OR**
    - Used as a rechallenge if pemetrexed-based treatment was administered first-line with good response

Non-Squamous Non-Small Cell Lung Cancer (NS-NSCLC) † ‡ [1-4,8-10,12,13,23,29,31,50e,51e,54e,56e-58e,81e-83e,91e-95e,98e,101e]

- Used only 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 nivolumab and either cisplatin or carboplatin as neoadjuvant therapy for resectable (tumors ≥ 4 cm or node positive) disease; **OR**
- Used in combination with pembrolizumab and cisplatin as neoadjuvant therapy for resectable (tumors ≥ 4 cm or node positive) disease; **OR**
- Used in combination with durvalumab and either cisplatin or carboplatin as neoadjuvant therapy for resectable (tumors ≥ 4 cm or node positive) disease; **OR**
- 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 in combination with cemiplimab and either cisplatin or carboplatin; **OR**
  - Used in combination with osimertinib as first-line therapy for EGFR exon 19 deletion or exon 21 L858R mutation positive disease; **OR**
  - Used in combination with amivantamab and carboplatin as first-line therapy for EGFR exon 20 insertion mutation positive disease; **OR**

- Used in combination with amivantamab and carboplatin following disease progression on osimertinib for EGFR exon 19 deletion or exon 21 L858R mutation positive disease; **OR**
- Used in combination with pembrolizumab and either cisplatin or carboplatin; **OR**
- Used in combination with tremelimumab, durvalumab, and either cisplatin or carboplatin; **OR**
- Used in combination with nivolumab, ipilimumab, and either cisplatin or carboplatin; **OR**
- Used as a single agent; **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, 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 platinum-based therapy

****** *Note: Actionable molecular genomic biomarkers include EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, and ERBB2 (HER2). Complete genotyping for EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, and ERBB2 (HER2), via biopsy and/or plasma testing. If a clinically actionable marker is found, it is reasonable to start therapy based on the identified marker. Treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.*
¥ *May also be used for patients with KRAS G12C mutation positive tumors.*

Thymomas ‡ [4,15,16,26,68e]

- Used as a single agent; **AND**
- Used as second-line therapy; **AND**
- Patient has unresectable or metastatic disease

Ovarian, Fallopian Tube, and Primary Peritoneal Cancer ‡ [4,14,25,74e,75e]

- Used as a single agent; **AND**
- Patient has platinum-resistant disease; **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

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.

§ Genomic Aberration/Mutational Driver Targeted Therapies (Note: *not all inclusive, refer to guidelines for appropriate use*)			
EGFR exon 19 deletion or exon 21 L858R tumors	*EGFR* S768I, L861Q, and/or G719X mutation positive tumors	*EGFR* exon 20 insertion mutation positive tumors	*NTRK1/2/3* gene fusion positive tumors
– Afatinib – Erlotinib – Dacomitinib – Gefitinib – Osimertinib – Amivantamab	– Afatinib – Erlotinib – Dacomitinib – Gefitinib – Osimertinib – Amivantamab	– Amivantamab	– Larotrectinib – Entrectinib – Repotrectinib
ALK rearrangement-positive tumors	*ROS1* rearrangement-positive tumors	*BRAF* V600E-mutation positive tumors	*ERBB2 (HER2)* mutation positive tumors
– Alectinib – Brigatinib – Ceritinib – Crizotinib – Lorlatinib	– Ceritinib – Crizotinib – Entrectinib – Lorlatinib – Repotrectinib	– Dabrafenib ± trametinib – Encorafenib + binimetinib – Vemurafenib	– Fam-trastuzumab deruxtecan-nxki – Ado-trastuzumab emtansine
PD-L1 tumor expression ≥ 1%	*MET* exon-14 skipping mutations	*RET* rearrangement-positive tumors	*KRAS G12C* mutation positive tumors
– Pembrolizumab – Atezolizumab – Nivolumab + ipilimumab – Cemiplimab – Tremelimumab + durvalumab	– Capmatinib – Crizotinib – Tepotinib	– Selpercatinib – Cabozantinib – Pralsetinib	– Sotorasib – Adagrasib

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

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**

Mesothelioma (PM) [27,30]

- Coverage may NOT be renewed when used in combination with bevacizumab AND either cisplatin or carboplatin

Thymomas [16]

- Coverage may NOT be renewed

V. Dosage/Administration [1-3,11,14,16,17,27,29-34,37-40]

Indication	Dose
Non-Squamous NSCLC	Administer up to 500 mg/m^2 intravenously every 21 days
Mesothelioma (peritoneal and pleural)	Administer 500 mg/m^2 intravenously every 21 days – For 6 cycles only when used in combination with bevacizumab AND either cisplatin or carboplatin – All others until disease progression or unacceptable toxicity
Ovarian, Fallopian Tube, and Primary Peritoneal Cancer	Administer up to 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 or until disease progression or unacceptable toxicity
• Supplement with oral folic acid and intramuscular vitamin B12. • 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 administer in patients with CrCl <45 mL/min.	

VI. Billing Code/Availability Information

Product Formulation	Drug	Manufacturer	Type	HCPCS Code	NDC
Pemetrexed Disodium Hemipentahydrate Solution for injection	Pemrydi RTU 100 mg/10 mL SDV Ψ Pemrydi RTU 500 mg/50 mL SDV Ψ Pemrydi RTU 1000 mg/100 mL SDV Ψ	Amneal	Brand	J9324	70121-2453-xx 70121-2461-xx 70121-2462-xx
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	Hospira	Brand	J9294	00409-1060-xx 00409-1061-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 850 mg/34mL inj. SDV Ψ	Accord	Brand	J9296	16729-0522-xx
	Pemetrexed 1000 mg/40 mL inj. SDV Ψ	Accord	Brand	J9296	16729-0522-xx
		Hospira	Brand	J9294	00409-3532-xx
	Pemfexy 500 mg/20 mL inj. MDV	Eagle	Brand	J9304	42367-0531-xx

Pemetrexed Solution for injection	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 Lyophilisate for injection	Pemetrexed 100 mg powder for inj. SDV Ψ	Hospira	Brand	J9323	00409-1060-xx
	Pemetrexed 500 mg powder for inj. SDV Ψ				00409-1061-xx
Pemetrexed Dipotassium for injection	Axtle 100 mg powder for inj. SDV Ψ	Avyxa	Brand	J9292	83831-0111-xx
	Axtle 500 mg powder for inj. SDV Ψ				83831-0112-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*

J9292 – Injection, pemetrexed (axtle), 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
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
J9999 – Injection, pemetrexed various (shipla, etc.), 10 mg

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
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

ICD-10	ICD-10 Description
C45.0	Mesothelioma of pleura
C45.1	Mesothelioma of peritoneum
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
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)

The preceding information is intended for non-Medicare coverage determinations. 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 Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used

to search for NCD, LCD, or LCA documents: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications, including any preceding information, may be applied 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		
Jurisdictio	**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, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
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 (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA
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