

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: 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 disodium 750 mg powder for injection: 2 vials every 21 days
- Pemetrexed disodium 1000 mg powder for injection: 2 vials every 21 days
- Pemetrexed disodium 100 mg/4 mL solution for injection: 4 vials every 21 days
- Pemetrexed disodium 500 mg/20 mL solution for injection: 4 vials every 21 days
- Pemetrexed disodium 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) † ⊕ 1-6,10,26,31,79e,80e

- Used as induction therapy; **AND**
 - Used in combination with cisplatin or carboplatin (if cisplatin ineligible) in patients has with epithelioid histology; **OR**
- Used as first-line therapy; **AND**
 - Used in combination with bevacizumab and cisplatin followed by single-agent maintenance bevacizumab (preferred) as first-line systemic therapy; **OR**
 - Used in combination with cisplatin or carboplatin (if cisplatin ineligible) for resected or recurrent disease; **OR**
- Used as subsequent therapy; **AND**
 - Used in combination with cisplatin or carboplatin (if cisplatin ineligible), with or without bevacizumab, if immunotherapy was administered as first-line treatment; **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: 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 in combination with carboplatin or cisplatin; **OR**
- Used in combination with cisplatin and nivolumab as neoadjuvant therapy for resectable (tumors \geq 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 pembrolizumab and either cisplatin or carboplatin; **AND**
 - PD-L1 \geq 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 \geq 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 single-agent therapy; **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 PD-L1 $\geq 1\%$ tumors that have negative actionable molecular biomarkers*
 - First-line therapy for 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
 - Subsequent therapy for first progression after initial systemic 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 continuation or switch maintenance therapy in patients who have achieved tumor response or stable disease following initial therapy (*Note: Continuation maintenance therapy may also be given in combination with bevacizumab or pembrolizumab*)

** 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 (Epithelial Ovarian/Fallopian Tube/Primary Peritoneal Cancer) † 3,13,24,74e,75e

- Used as single-agent therapy; **AND**
 - 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**
 - 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*)

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); Ⓞ 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	ERBB2 (HER2) mutation positive tumors
<ul style="list-style-type: none"> – Afatinib – Erlotinib – Dacomitinib – Gefitinib – Osimertinib – Amivantamab (exon-20 insertion) – Mobocertinib 	<ul style="list-style-type: none"> – Alectinib – Brigatinib – Ceritinib – Crizotinib – Lorlatinib 	<ul style="list-style-type: none"> – Ceritinib – Crizotinib – Entrectinib – Lorlatinib 	<ul style="list-style-type: none"> – Dabrafenib ± trametinib – Vemurafenib 	<ul style="list-style-type: none"> – Larotrectinib – Entrectinib 	<ul style="list-style-type: none"> – Fam-trastuzumab deruxtecan-nxki – Ado-trastuzumab emtansine

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(<i>exon-20 insertion</i>)					
PD-L1 tumor expression \geq 1%	PD-L1 tumor expression \geq 50%	<i>MET</i> exon-14 skipping mutations	<i>RET</i> rearrangement-positive tumors	<i>KRAS G12C</i> mutation positive tumors	
<ul style="list-style-type: none"> – Pembrolizumab – Atezolizumab – Nivolumab + ipilimumab 	<ul style="list-style-type: none"> – Pembrolizumab – Atezolizumab – Nivolumab + ipilimumab – Cemiplimab 	<ul style="list-style-type: none"> – Capmatinib – Crizotinib – Tepotinib 	<ul style="list-style-type: none"> – Selpercatinib – Cabozantinib – Pralsetinib 	<ul style="list-style-type: none"> – 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**

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 ^{1,2,13,15,16,26,28-30}

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 <ul style="list-style-type: none"> – 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
<ul style="list-style-type: none"> • 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 dose in patients with CrCl <45 mL/min 	

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VI. Billing Code/Availability Information

Product Formulation	Drug	Manufacturer	Type	HCPCS Code	NDC
Pemetrexed Disodium Lyophilisate for inj.	Alimta 100 mg powder for inj. SDV *	Lilly	Brand	J9305	00002-7640-xx
	Alimta 500 mg powder for inj. SDV *				00002-7623-xx
	Pemetrexed 100 mg powder for inj. Ψ	Hospira	Brand	J9305	00409-1060-xx
	Pemetrexed 500 mg powder for inj. Ψ				00409-1061-xx
	Pemetrexed 1000 mg powder for inj. Ψ				00409-1062-xx
Pemetrexed 750 mg powder for inj.*	N/A	Generic	J9305	N/A	
Pemetrexed 1000 mg powder for inj.*					
Pemetrexed Disodium Solution for injection	Pemetrexed 100mg/4mL inj. SDV Ψ	Sandoz	Brand	J9305	00781-3518-xx
		Accord			16729-0522-xx
	Pemetrexed 500mg/20mL inj. SDV Ψ	Hospira	Brand	J9305	00409-2188-xx
		Sandoz			00781-3519-xx
		Accord			16729-0522-xx
	Pemetrexed 1000mg/40mL inj. SDV Ψ	Hospira	Brand	J9305	00409-3532-xx
Accord		16729-0522-xx			
Pemetrexed Solution for injection	Pemfexy 500 mg/20 mL inj. MDV	Eagle.	Brand	J9304	42367-0531-xx
	Pemetrexed 100mg/4mL inj. SDV Ψ	Hospira	Brand	J9305	00409-1045-xx
		Teva		J9314	00480-4516-xx
	Pemetrexed 500mg/20mL inj. SDV Ψ	Teva	Brand	J9314	00480-4514-xx
Pemetrexed 1000mg/40mL inj. SDV Ψ	Teva	Brand	J9314	00480-4515-xx	
*Multiple manufacturers produce ANDA generics					
Ψ Approved by the FDA as a 505(b)(2) NDA of the innovator product					
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 (Effective 1/1/2023)					

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

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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

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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