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

Document Number: IC-0007

Last Review Date: 06/04/2024
Date of Origin: 07/20/2010
Dates Reviewed: 09/2010, 12/2010, 03/2011, 06/2011,0 9/2011, 12/2011, 03/2012, 06/2012, 09/2012, 12/2012, 03/2013, 06/2013, 09/2013, 12/2013, 03/2014, 06/2014, 09/2014, 12/2014, 03/2015, 05/2015, 08/2015, 11/2015, 02/2016, 05/2016, 08/2016, 11/2016, 02/2017, 05/2017, 08/2017, 11/2017, 02/2018, 05/2018, 09/2018, 12/2018, 03/2019, 06/2019, 09/2019, 12/2019, 03/2020, 06/2020, 09/2020, 12/2020, 03/2021, 06/2021, 09/2021, 12/2021, 03/2022, 06/2022, 09/2022, 12/2022, 03/2023, 07/2023, 09/2023, 12/2023, 03/2024, 06/2024

I. Length of Authorization [15,26,28-30]

Coverage will be provided for 6 months and may be renewed, unless otherwise specified.

- Thymomas and Thymic Carcinomas: Coverage will be provided for six (6) cycles and may NOT be renewed.
- Mesothelioma (including PeM, PM, pericardial mesothelioma and tunica vaginalis testis mesothelioma) 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):
  - Primary CNS Lymphoma, Cervical Cancer, Vaginal Cancer, and Ovarian Cancer: 225 billable units every 21 days
  - Leptomeningeal Metastases from NSCLC: 5 billable units every 28 days
  - Thymomas and Thymic Carcinomas: 125 billable units every 21 days
  - All other indications: 125 billable units every 21 days
- Pemetrexed (all other manufacturers) (100 mg, 500 mg, 750 mg, 850mg, and 1000 mg SDV):
  - Primary CNS Lymphoma, Cervical Cancer, Vaginal Cancer, and Ovarian Cancer: 230 billable units every 21 days
  - Leptomeningeal Metastases from NSCLC: 10 billable units every 28 days
  - Thymomas and Thymic Carcinomas: 130 billable units every 21 days
  - All other indications: 130 billable units every 21 days

III. Initial Approval Criteria [1-3]

Coverage is provided in the following conditions:

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

Central Nervous System (CNS) Cancers ‡ [4,17,28,34]

- 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 (NSCLC); **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 ‡ [4,35]

- 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

Peritoneal* Mesothelioma (PeM) ‡ [4,30]

- Used as a single agent OR in combination with cisplatin or carboplatin (if cisplatin ineligible), with or without bevacizumab; **AND**
  - 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; **OR**
  - Used as first-line therapy; **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**
    - 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

** 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*

Pleural* Mesothelioma (PM) † ‡ Φ [1-7,11,27]

- 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); **OR**
  - Used as a single agent OR in combination with cisplatin or carboplatin (if cisplatin ineligible); **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

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

Non-Squamous Non-Small Cell Lung Cancer (NS-NSCLC) †‡ [1-4,8-10,12,13,29,31]

- 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, 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, 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 and Thymic Carcinomas ‡ [4,15,16,26]

- Used as a single agent; **AND**
  - Patient is unable to tolerate first-line combination regimens; **AND**
    - Used as preoperative systemic therapy for surgically resectable disease if R0 resection is considered uncertain; **OR**
    - Used as postoperative treatment after R1* (microscopic residual tumor) or R2 (macroscopic residual tumor) resection; **OR**
    - Used as first-line therapy for recurrent, advanced, or metastatic disease; **OR**
  - Used as second-line therapy; **AND**
    - Patient has unresectable or metastatic disease

**Note: applies to thymic carcinoma only*

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

- 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

Vaginal Cancer ‡ [4,36]

- Used as a single agent; **AND**
- Used as subsequent therapy for recurrent or metastatic disease

§ 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
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 (including PeM, PM, pericardial mesothelioma and tunica vaginalis testis mesothelioma) [27,30]

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

Thymomas and Thymic Carcinomas [16]

- Coverage may NOT be renewed

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

Indication	Dose
Non-Squamous NSCLC	Administer up to 500 mg/m^2 intravenously every 21 days
Mesotheliomas (peritoneal, pleural, pericardial and tunica vaginalis testis)	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 Cancer, Cervical Cancer, Vaginal Cancer	Administer 900 mg/m^2 intravenously every 21 days, until disease progression or unacceptable toxicity
Thymomas and Thymic Carcinomas	Administer 500 mg/m^2 intravenously every 21 days for a maximum of 6 cycles or until disease progression or unacceptable toxicity
CNS Cancers	<u>Primary CNS Lymphoma</u> Administer 900 mg/m^2 intravenously every 21 days, until disease progression or unacceptable toxicity <u>Leptomeningeal metastases from EGFR mutation-positive NSCLC</u> Administer 50 mg intrathecally every 28 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 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	Lilly	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
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				00409-1061-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*

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

1. Alimta [package insert]. Indianapolis, IN; Eli Lilly; May 2023. Accessed April 2024.
2. Pemfexy [package insert]. Woodcliff Lake, NJ; Eagle Pharmaceuticals, Inc; December 2022. Accessed May 2024.

3. Pemrydi RTU [package insert]. Bridgewater, NJ; Amneal Pharmaceuticals LLC; June 2023. Accessed May 2024.
4. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for pemetrexed. National Comprehensive Cancer Network, 2024. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed April 2024.
5. Castagneto B, Botta M, Aitini E, et al, "Phase II Study of Pemetrexed in Combination With Carboplatin in Patients With Malignant Pleural Mesothelioma (MPM)," Ann Oncol, 2008, 19(2):370-3.
6. Ceresoli GL, Zucali PA, Favaretto AG, et al, "Phase II Study of Pemetrexed plus Carboplatin in Malignant Pleural Mesothelioma," J Clin Oncol, 2006, 24(9):1443-8.
7. Taylor P, Castagneto B, Dark G, et al, "Single-Agent Pemetrexed for Chemonaïve and Pretreated Patients With Malignant Pleural Mesothelioma: Results of an International Expanded Access Program," J Thorac Oncol, 2008, 3(7):764-71
8. Ciuleanu T, Brodowicz T, Zielinski C, et al, "Maintenance Pemetrexed Plus Best Supportive Care versus Placebo Plus Best Supportive Care for Non-Small-Cell Lung Cancer: A Randomised, Double-Blind, Phase 3 Study," Lancet, 2009, 374(9699):1432-40.
9. Grønberg BH, Bremnes RM, Fløtten O, et al, "Phase III Study by the Norwegian Lung Cancer Study Group: Pemetrexed Plus Carboplatin Compared With Gemcitabine Plus Carboplatin as First-Line Chemotherapy in Advanced Non-Small-Cell Lung Cancer," J Clin Oncol, 2009, 27(19):3217-24.
10. Hanna N, Shepherd FA, Fossella FV, et al, "Randomized Phase III Trial of Pemetrexed versus Docetaxel in Patients With Non-Small-Cell Lung Cancer Previously Treated With Chemotherapy," J Clin Oncol, 2004, 22(9):1589-97.
11. Jassem J, Ramlau R, Santoro A, et al, "Phase III Trial of Pemetrexed Plus Best Supportive Care Compared With Best Supportive Care in Previously Treated Patients With Advanced Malignant Pleural Mesothelioma," J Clin Oncol, 2008, 26(10):1698-704.
12. Scagliotti GV, Parikh P, von Pawel J, et al, "Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naive Patients With Advanced-Stage Non-Small-Cell Lung Cancer," J Clin Oncol, 2008, 26(21):3543-51.
13. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016;17(11):1497-1508.

14. Miller DS, Blessing JA, Krasner CN, et al. Phase II Evaluation of Pemetrexed in the Treatment of Recurrent or Persistent Platinum-Resistant Ovarian or Primary Peritoneal Carcinoma: A Study of the Gynecologic Oncology Group. J Clin Oncol, 2009, 27(16):2686-91.
15. Liang Y, Padda SK, Riess JW, et al. Pemetrexed in patients with thymic malignancies previously treated with chemotherapy. Lung Cancer. 2015 Jan;87(1):34-8.
16. Gbolahan OB, Porter RF, Salter JT, et al. A Phase II Study of Pemetrexed in Patients with Recurrent Thymoma and Thymic Carcinoma. J Thorac Oncol. 2018 Dec;13(12):1940-1948.
17. Raizer JJ, Rademaker A, Evens AM, et al. Pemetrexed in the treatment of relapsed/refractory primary central nervous system lymphoma. Cancer. 2012 Aug 1;118(15):3743-8.
18. Fahrenbruch R, Kintzel P, Bott AM, et al. Dose Rounding of Biologic and Cytotoxic Anticancer Agents: A Position Statement of the Hematology/Oncology Pharmacy Association. J Oncol Pract. 2018 Mar;14(3):e130-e136.
19. Hematology/Oncology Pharmacy Association (2019). Intravenous Cancer Drug Waste Issue Brief. Retrieved from http://www.hoparx.org/images/hopa/advocacy/Issue-Briefs/Drug_Waste_2019.pdf
20. Bach PB, Conti RM, Muller RJ, et al. Overspending driven by oversized single dose vials of cancer drugs. BMJ. 2016 Feb 29;352:i788.
21. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med. 2018;378(22):2078-2092. doi:10.1056/NEJMoa1801005.
22. Wu YL, Lu S, Cheng Y, et al. Efficacy and safety of pemetrexed/cisplatin versus gemcitabine/cisplatin as first-line treatment in Chinese patients with advanced nonsquamous non-small cell lung cancer. Lung Cancer. 2014;85(3):401-407. doi:10.1016/j.lungcan.2014.07.007.
23. Paz-Ares L, de Marinis F, Dediu M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol. 2012;13(3):247-255. doi:10.1016/S1470-2045(12)70063-3.
24. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol. 2003;21(14):2636-2644. doi:10.1200/JCO.2003.11.136.
25. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer Version 2.2024. National Comprehensive Cancer Network, 2024. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed May 2024.

26. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Thymomas and Thymic Carcinomas Version 1.2024. National Comprehensive Cancer Network, 2024. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed May 2024.
27. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Mesothelioma: Pleural Version 1.2024. National Comprehensive Cancer Network, 2024. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed May 2024.
28. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Central Nervous System Cancers Version 1.2023. National Comprehensive Cancer Network, 2024. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed May 2024.
29. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer Version 5.2024. National Comprehensive Cancer Network, 2024. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed May 2024.
30. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Mesothelioma: Peritoneal Version 1.2024. National Comprehensive Cancer Network, 2024. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed May 2024.
31. Forde P, Spicer J, Provencio M, et.al. Abstract CT003: Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo as neoadjuvant treatment (tx) for resectable (IB-IIIA) non-small cell lung cancer (NSCLC) in the phase 3 CheckMate 816 trial. Cancer Res (2021) 81 (13_Supplement): CT003.https://doi.org/10.1158/1538-7445.AM2021-CT003.
32. Miller DS, Blessing JA, Bodurka DC, et al. Evaluation of pemetrexed (Alimta, LY231514) as second line chemotherapy in persistent or recurrent carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol. 2008 Jul;110(1):65-70. doi: 10.1016/j.ygyno.2008.03.009.
33. Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a

randomised, controlled, open-label, phase 3 trial. Lancet. 2016 Apr 2;387(10026):1405-1414. doi: 10.1016/S0140-6736(15)01238-6.

34. Fan C, Zhao Q, Li L, et al. Efficacy and Safety of Intrathecal Pemetrexed Combined With Dexamethasone for Treating Tyrosine Kinase Inhibitor-Failed Leptomeningeal Metastases From EGFR-Mutant NSCLC-a Prospective, Open-Label, Single-Arm Phase 1/2 Clinical Trial (Unique Identifier: ChiCTR1800016615). J Thorac Oncol. 2021 Aug;16(8):1359-1368. doi: 10.1016/j.jtho.2021.04.018.
35. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Cervical Cancer Version 3.2024. National Comprehensive Cancer Network, 2024. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed May 2024.
36. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Vaginal Cancer Version 1.2025. National Comprehensive Cancer Network, 2024. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed May 2024.

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

ICD-10	ICD-10 Description
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
C52	Malignant neoplasm of vagina
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

ICD-10	ICD-10 Description
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
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		
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
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)

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
15	KY, OH	CGS Administrators, LLC