 Approved Revision: Do Not Implement Until 6/2/21

Pemetrexed (Alimta®)

NDC CODE(S) 00002-7640-XX ALIMTA 100MG Solution Reconstituted (ELI LILLY & CO.)
00002-7623-XX ALIMTA 500MG Solution Reconstituted (ELI LILLY & CO.)

DESCRIPTION

Pemetrexed is a folate analog metabolic inhibitor. It interferes with cell metabolic processes by disrupting the folate-dependent processes required for cell replication by inhibiting the biosynthesis of thymidine and purine nucleotides. This prevents the formation of the DNA and RNA required for the growth and survival of both cancer and normal cells.

POLICY

- Pemetrexed for the treatment of the following is considered ***medically necessary*** if the medical appropriateness criteria are met: **(See Medical Appropriateness below.)**
  - Central nervous system cancers
  - Lung cancer
  - Mesothelioma
  - Ovarian Cancer
  - Thymomas and thymic carcinomas
- Pemetrexed for the treatment of other conditions/diseases is considered ***investigational***.

MEDICAL APPROPRIATENESS

INITIAL APPROVAL CRITERIA

Universal Criteria

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

Primary Central Nervous System (CNS) Lymphoma

- Used as a single agent as induction therapy in patients unsuitable for or intolerant to high-dose methotrexate (MTX); **OR**
- Used as single agent therapy for relapsed or refractory disease; **AND**
  - Patient received prior whole brain radiation therapy (RT); **OR**
  - Patient received a prior high-dose MTX-based regimen without prior radiation therapy; **OR**
  - Used in combination with whole brain RT or involved field RT in patients who received a prior high-dose MTX-based regimen without prior RT with either no response or short response (<12 month duration) to prior regimen; **OR**
  - Patient received prior high-dose chemotherapy with stem cell rescue

Malignant Pleural* Mesothelioma (MPM)

- Used in combination with cisplatin or carboplatin; **AND**
  - Patient has stage IIIB or IV disease, sarcomatoid, or medically inoperable tumors and used as initial first-line therapy with or without bevacizumab; **OR**
  - Patient has stage I-IIIA disease with epithelioid or biphasic histology; **AND**
    - Used as induction therapy; **OR**

  - Used as first-line therapy with or without bevacizumab for unresectable disease; **OR**
  - Patient has resected disease not treated with induction chemotherapy; **OR**
- Used as a single agent; **AND**
  - ~~Used as initial first-line therapy for~~ Patient has ~~clinical~~ stage IIIB or IV disease, sarcomatoid, or medically inoperable tumors and used as first-line therapy; OR
  - Patient has stage I-IIIA disease with epithelioid or biphasic histology; **AND**
    - Used as first-line therapy for unresectable disease; **OR**
    - Patient has resected disease not previously treated with induction chemotherapy; **OR**
  - Used as subsequent therapy, if not administered first-line; **OR**
  - Used as a re-challenge, if pemetrexed was administered first-line with a good sustained response at the time initial chemotherapy was interrupted;

**peritoneal, pericardial, and tunica vaginalis testis mesothelioma will be evaluated on a case-by-case basis*

Non-Squamous Non-Small Cell Lung Cancer (NSNSCLC)

- Used in combination with carboplatin or cisplatin; **AND**
  - Used as induction, neoadjuvant, or adjuvant therapy; **OR**
  - Used as concurrent chemoradiation for locoregional recurrence or symptomatic local disease in the mediastinal lymph nodes or for superior vena cava obstruction; **OR**
    - Used as initial therapy as definitive concurrent chemoradiation for unresectable, advanced, or metastatic 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 are EGFR, ALK, ROS1, BRAF, MET exon 14 skipping mutation, and RET rearrangement negative*; **AND**
      - Used in combination with pembrolizumab and either carboplatin or cisplatin in patients with PS 0-2; **OR**
      - Used in combination with nivolumab, ipilimumab, and either carboplatin or cisplatin in patients with PS 0-2; **OR**
    - Used for one of the following:
      – PD-L1 <1% and EGFR, ALK, ROS1, BRAF, MET exon 14 skipping mutation, and RET rearrangement negative* tumors
      – BRAF V600E-mutation, NTRK gene fusion, MET exon-14 skipping mutation, or RET rearrangement positive tumors; **AND**
      - Used as a single agent in patients with PS 2; **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; **OR**
      - Used in combination with carboplatin in patients with PS 0-2; **OR**
      - Used in combination with nivolumab, ipilimumab, and either carboplatin or cisplatin in patients with PS 0-1; **OR**
      - Used in combination with bevacizumab and either cisplatin or carboplatin in patients with PS 0-1; **OR**
  - Used as subsequent therapy; **AND**
    - Used as a single-agent (if not previously given) in patients with a PS 0-2; **OR**
    - Used for one of the following:

- EGFR, ALK, or ROS1 positive tumors who received prior targeted therapy§ for those aberrations
- BRAF V600E-mutation, NTRK gene fusion, MET exon-14 skipping mutation, or RET rearrangement positive tumors
- PD-L1 ≥ 1% tumors that are EGFR, ALK, ROS1, BRAF, MET exon 14 skipping mutation, and RET rearrangement negative* 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 (excluding use in patients who have received prior PD-1/PD-L1 inhibitor therapy); **OR**
- Used in combination with cisplatin in patients with PS 0-1; **OR**
- Used in combination with carboplatin in patients with PS 0-2; **OR**
- Used in combination with nivolumab, ipilimumab, and either carboplatin or cisplatin in patients with PS 0-1 (excluding use in patients who have received prior PD-1/PD-L1 inhibitor therapy); **OR**
- Used in combination with bevacizumab and either cisplatin or carboplatin in patients with PS 0-1; **OR**

- Used as subsequent therapy; **AND**
  - Used as a single-agent (if not previously given) in patients with a PS 0-2; **OR**
  - Used for one of the following:
    - EGFR, ALK, or ROS1 positive tumors who received prior targeted therapy§ for those aberrations
    - BRAF V600E-mutation, NTRK gene fusion, MET exon-14 skipping mutation, or RET rearrangement positive tumors
    - PD-L1 ≥ 1% tumors that are EGFR, ALK, ROS1, BRAF, MET exon 14 skipping mutation, and RET rearrangement negative* 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 (excluding use in patients who have received prior PD-1/PD-L1 inhibitor therapy); **OR**
    - Used in combination with cisplatin in patients with PS 0-1; **OR**
    - Used in combination with carboplatin in patients with PS 0-2; **OR**
    - Used in combination with nivolumab, ipilimumab, and either carboplatin or cisplatin in patients with PS 0-1 (excluding use in patients who have received prior PD-1/PD-L1 inhibitor therapy); **OR**
    - Used in combination with bevacizumab and either cisplatin or carboplatin in patients with PS 0-1; **OR**
- 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; **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: If there is insufficient tissue to allow testing for all of the EGFR, ALK, ROS1, BRAF, 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.*

Thymomas/Thymic Carcinoma

- Used for second-line treatment of unresectable or metastatic disease; **AND**

- Used as a single agent

Ovarian Cancer (epithelial ovarian/fallopian tube/primary peritoneal cancer)

- Used for disease progression, stable or persistent disease (if not on maintenance therapy), or disease relapse; **AND**
- Patient is not experiencing an immediate biochemical relapse (i.e., rising CA-125 and no radiographic evidence of disease); **AND**
- Used as a single agent

§Genomic Aberration/Mutational Driver Targeted Therapies (Note: ***not all inclusive, refer to guidelines for appropriate use***)
Sensitizing *EGFR* mutation-positive tumors ▫ Afatinib ▫ Erlotinib ▫ Dacomitinib ▫ Gefitinib ▫ Osimertinib
ALK rearrangement-positive tumors ▫ Alectinib ▫ Brigatinib ▫ Ceritinib ▫ Crizotinib ▫ Lorlatinib
ROS1 rearrangement-positive tumors ▫ Ceritinib ▫ Crizotinib ▫ Entrectinib
BRAF V600E-mutation positive tumors ▫ Dabrafenib ± Trametinib ▫ Vemurafenib
NTRK Gene Fusion positive tumors ▫ Larotrectinib ▫ Entrectinib
PD-1/PD-L1 expression-positive tumors (≥1%) ▫ Pembrolizumab ▫ Atezolizumab ▫ Nivolumab ± ipilimumab
MET Exon-14 skipping mutations ▫ Capmatinib ▫ Crizotinib
RET rearrangement-positive tumors ▫ Selpercatinib ▫ Cabozantinib ▫ Vandetanib

RENEWAL CRITERIA

- Patient continues to meet indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in initial criteria; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: bone marrow suppression (e.g., neutropenia, febrile neutropenia, thrombocytopenia, anemia), renal impairment (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 Initial Approval Criteria

MPM

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

Thymomas/Thymic Carcinoma

- May not be renewed

DOSAGE/ADMINISTRATION

INDICATION	DOSE
Non-Squamous NSCLC ~~Malignant Pleural Mesothelioma~~	Administer 500 mg/m2 intravenously every 21 days, until disease progression or unacceptable toxicity
Malignant Pleural Mesothelioma	Administer 500 mg/m2 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
Primary CNS Lymphoma, Ovarian Cancer	Administer 900 mg/m2 intravenously every 21 days, until disease progression or unacceptable toxicity
Thymomas/Thymic Carcinoma	Administer 500 mg/m2 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 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	

LENGTH OF AUTHORIZATION

Coverage will be provided for six 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.
- MPM: Coverage will be provided for six 21-day cycles and may not be renewed when used in combination with platinum therapy and bevacizumab.

DOSAGE LIMITS

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

- CNS Lymphoma and Ovarian Cancer: 230 billable units every 21 days
- All other indications: 130 billable units every 21 days

APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

BlueCross BlueShield of Tennessee's Medical Policy complies with Tennessee Code Annotated Section 56-7-2352 regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

IMPORTANT REMINDER

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the Medical Policy and a health plan, the express terms of the health plan will govern.

ADDITIONAL INFORMATION

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).

SOURCES

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EFFECTIVE DATE 6/2/2021

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