**I. PURPOSE**

To define and describe the accepted indications for Alimta (pemetrexed) usage in the treatment of cancer.

**II. DEFINITIONS**

**Alimta (pemetrexed):** is a pyrimidine-based cytotoxic chemotherapy classified as an anti-folate. Alimta (pemetrexed) disrupts folate-dependent metabolic processes essential for cell replication. It inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), glycinamide ribonucleotide formyltransferase (GARFT), and aminoimidazolecarboxamide ribonucleotide formyltransferase (AICARFT), the enzymes involved in folate metabolism and DNA synthesis, resulting in inhibition of purine and thymidine nucleotide and protein synthesis.

Alimta (pemetrexed) is FDA approved for the initial, subsequent, or maintenance treatment of patients with non-squamous non-small cell lung cancer (NSCLC) or for the treatment of mesothelioma. Non-FDA approved indications include:

- Bladder Cancer
- Ovarian Cancer

Alimta (pemetrexed) is available as 100 mg and 500 mg vials.

**III. POLICY**

New Century is responsible for processing all medication requests from network ordering providers. Medications not authorized by New Century may be deemed as not approvable and therefore not reimbursable.

Treatment request outside the approved FDA manufacturer labeling or CMS approved compendia must follow CMS Medicare Benefit Policy Manual Chapter 15. If references are not produced, delays may occur to the processing of such request.
Inclusion Criteria: Alimta (pemetrexed) may be considered medically necessary when any of the following selection criteria is met:

1. **Non-Small Cell Lung Cancer (NSCLC)**
   a. The member has non-squamous NSCLC and Alimta (pemetrexed) is being used for **ONE** of the following:
      i. Resectable/unresectable (Stage IIA, IIB, IIIA)
      ii. As induction, neoadjuvant, or adjuvant chemotherapy in combination with cisplatin or carboplatin.
      iii. Unresectable (Stage IIIB, IV) with **ONE** of the following:
         1. As a single agent for members with performance status (PS) 2, in combination with carboplatin and pembrolizumab (if pembrolizumab not previously given) or in combination with cisplatin/carboplatin ± bevacizumab for PS 0-1, or in combination with carboplatin alone for PS 0-2.
            a. First line for EGFR, ALK, ROS1, BRAF negative or unknown, and PD-L1 <50% or unknown OR
            b. Subsequent therapy (if not already given) with prior exposure to erlotinib, afatanib, gefitinib, or crizotinib
            c. Subsequent therapy for PD-L1 expression-positive (≥50%) tumors and EGFR, ALK, ROS1, and BRAF negative or unknown.
      2. Continuation or switch maintenance therapy as a single agent or in combination with bevacizumab if bevacizumab previously used with a first-line chemotherapy regimen OR
      3. Continuation maintenance therapy in combination with pembrolizumab following first-line therapy with pembrolizumab/pemetrexed and either cisplatin or carboplatin.

2. **Mesothelioma**
   a. The member has malignant pleural mesothelioma and Alimta (pemetrexed) is as the following:
      i. As a single agent or in combination with cisplatin or carboplatin, or in combination with bevacizumab and cisplatin/carboplatin for unresectable stage I-III disease **OR**
      ii. In combination with cisplatin for resectable stage I-III disease as induction therapy **OR**
      iii. As a single agent or in combination with cisplatin or carboplatin in resectable stage I-III disease in patients not treated with induction chemotherapy **OR**
      iv. Subsequent therapy as a single agent.

3. **Bladder Cancer**
a. The member has advanced transitional cell bladder cancer and Alimta (pemetrexed) is being used as second-line therapy as a single agent for metastatic disease.

4. Ovarian Cancer
a. The member has recurrent ovarian cancer and Alimta (pemetrexed) is being used as a single agent for persistent disease or recurrence.

Exclusion Criteria: Alimta (pemetrexed) is not considered medically necessary when any of the following selection criteria is met:

1. For member with NSCL, Alimta (pemetrexed) is being used for any of the following:
   • Creatinine clearance less than 45 ml/min
   • Squamous cell histology
   • In member with PS > 2
   • History of hemoptysis
   • As adjuvant therapy for stage IA and IB NSCLC
   • Being used without pretreatment medications (i.e. oral dexamethasone, folic acid or a multivitamin, and vitamin B12 injection)
   • Being used as second line treatment after disease progression on Alimta (pemetrexed) constituting treatment failure.

2. Alimta (pemetrexed) is being used in bladder cancer as initial treatment.

3. Alimta (pemetrexed) is being used in ovarian cancer without failure to first line platinum based therapy.

4. Dosing exceeds single dose limit of Alimta (pemetrexed) 500 mg/m².

5. Indications not supported by CMS recognized compendia or acceptable peer reviewed literature may be deemed as not approvable and therefore not reimbursable.

IV. PROCEDURE

Requests for Alimta (pemetrexed) shall be reviewed for appropriateness per FDA approved product labeling, the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) clinical guidelines, or CMS approved compendia.

1. Dosage and Administration

Recommended dose for NSCLC, mesothelioma, bladder cancer, and ovarian cancer: 500 mg/m² IV on Day 1 of each 21-day cycle. Members should receive oral dexamethasone 4 milligrams (or equivalent) twice daily for 3 days starting the day before pemetrexed treatment to decrease the risk of skin reactions. Additionally, oral folic acid or a multivitamin with folic acid (350 to 1000 micrograms (mcg)) once daily given 5 of 7 days prior to treatment, during, and for 21 days after treatment and intramuscular vitamin B12 1000 mcg beginning one week prior to pemetrexed and then given every 3 cycles thereafter on the same day as the pemetrexed infusion.

2. Dosage Adjustments
a. Renal impairment: no dosage adjustments are necessary for members with a creatinine clearance of 45 mL/min or greater; members with a creatinine clearance of less than 45
mL/min should not receive pemetrexed; exercise caution in members with creatinine clearance less than 80 mL/min administered pemetrexed concurrently with NSAID.

b. **Hepatic insufficiency**: hold treatment until resolution to less than or equal to baseline values; for grade 3/4 non-hematologic toxicities, (except mucositis) reduce the dose by 75% of the previous pemetrexed and cisplatin doses; pemetrexed therapy should be discontinued in any patient experiencing any non-hematologic grade 3/4 toxicity after 2 dose reductions.

c. **Neurotoxicity**: members experiencing any grade 2 NCI common toxicity should have the dose of cisplatin reduced by 50%; grade 3/4 neurotoxicity warrants discontinuation of therapy.

d. **Neutropenia**: reduce dose by 75% for both pemetrexed and cisplatin when nadir ANC is less than 500/mm$^3$ and nadir platelets 50,000/mm$^3$ or greater; discontinue if grade 3/4 toxicity occurs after 2 dose reductions.

e. **Non-hematologic toxicities**: hold treatment until resolution to less than or equal to baseline values; for grade 3/4 non-hematologic toxicities (except mucositis or any diarrhea requiring hospitalization) reduce resumed dose by 75% of the previous pemetrexed and cisplatin doses; grade 3/4 mucositis requires a 50% dose reduction of pemetrexed only; pemetrexed therapy should be discontinued in any patient experiencing any non-hematologic grade 3/4 toxicity after 2 dose reductions.

f. **Thrombocytopenia**: regardless of ANC nadir, reduce dose by 50% for both pemetrexed and cisplatin when the nadir platelet count is less than 50,000/mm$^3$ with bleeding and reduce dose by 75% for both pemetrexed and cisplatin when the nadir platelet count is less than 50,000/mm$^3$ without bleeding; discontinue if grade 3/4 toxicity occurs after 2 dose reductions.

3. **Monitoring**

   i. Monitor complete blood count regularly for nadir and recovery at baseline, before each dose, and on day 8 and 15 of each cycle. Members should not start new cycles unless the absolute neutrophil count is 1500 cells/mm$^3$ or greater and the platelet count is 100,000 cells/mm$^3$ or greater.

   ii. Assess renal function before each treatment cycle and periodically during treatment. Members should not start new cycles unless the creatinine clearance is 45 mL/min or greater.

   iii. Assess hepatic function periodically during treatment.

   iv. Monitor plasma homocysteine levels for elevations (marker for folate deficiency) which may be predictive of pemetrexed toxicity.

   v. Radiologic evidence of tumor regression (eg, CT scan, MR scan, X-ray, ultrasound) is indicative of efficacy.

   vi. Cutaneous reactions have been reported: corticosteroid pretreatment reduces incidence and severity.

   vii. Hematologic and gastrointestinal toxicities have occurred: prophylaxis with folic acid and vitamin B12 required.
V. APPROVAL AUTHORITY

1. Review – UM Department
2. Final Approval – UM Committee

VI. ATTACHMENTS

VII. REFERENCES