Clinical Criteria

Subject:	Pemetrexed Agents (Alimta, Pemfexy)		
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Overview

This document addresses the use of pemetrexed agents, including Alimta (pemetrexed disodium) and Pemfexy (pemetrexed), which are folate analog metabolic inhibitors. They work by inhibiting folate-dependent metabolic processes which disrupts cell replication.

The FDA approved indications for Alimta and Pemfexy include non-squamous (NSCLC) and malignant pleural mesothelioma.

Non-Small Lung Cancer

- In combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations (Alimta only*).
- In combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, (NSCLC).
- As a single agent for the maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.
- As a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy.

Malignant Pleural Mesothelioma

- In initial treatment, in combination with cisplatin, of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.

The FDA states neither Alimta nor Pemfexy are indicated for the treatment of patients with squamous cell, non-small cell lung cancer.

The National Comprehensive Cancer Network (NCCN) provides additional recommendations with a category 2A level of evidence for the use of pemetrexed in ovarian cancer, and thymomas and thymic carcinomas, and additional uses in NSCLC.

The NCCN panel includes category 1 recommendations for nonsquamous NSCLC continuation maintenance therapy for use of pembrolizumab in combination with pemetrexed if given first-line as part of pembrolizumab/carboplatin/pemetrexed or pembrolizumab/cisplatin/pemetrexed regimen. The NCCN panel also gives a category 1 and 2A recommendation for use of pemetrexed in combination with platinum-based therapy as adjuvant or neoadjuvant therapy in NSCLC (Kenmotsu 2020, Kreuter 2013, Zhang 2014).

The NCCN panel also gives a category 1 recommendation for use of pemetrexed in malignant mesothelioma as single agent, subsequent therapy.

The NCCN panel recommends that individuals with NSCLC be tested for actionable molecular markers, such as EGFR, ALK, ROS1, BRAF, NTRK, MET and RET mutations, before initiating first line therapy to help guide treatment. If there is insufficient tissue to allow testing for all of these markers, 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.

*The NCCN panel does not differentiate between Alimta and Pemfexy for any indication, including the use in NSCLC in combination with pembrolizumab and platinum therapy for initial treatment.

Other Uses

The National Comprehensive Cancer Network (NCCN) provides additional NCCN 2A recommendations individuals with NSCLC for pemetrexed and platinum-based therapy in combination with bevacizumab, followed by pemetrexed with bevacizumab as maintenance therapy if bevacizumab was a component of the first-line regimen. The recommendation is not included due to it based on a phase 3 trial (Patel 2013) and another randomized, open-label, phase 3 trail (Barlesi 2013) which did not demonstrate sufficient efficacy for the use of pemetrexed in combination with bevacizumab in those with non-squamous NSCLC. Thus, there is a lack of evidence in the peer-reviewed literature supporting the efficacy and safety of this chemotherapy combination, over single-agent treatment pemetrexed, as maintenance therapy in NSCLC. NCCN also provides a category 2A recommendation for pemetrexed as subsequent therapy in combination with platinum-based chemotherapy with or without bevacizumab (or bevacizumab biosimilar) if individual is PD-L1 positive (≥1%) and has a contraindication to anti-PD-L1/PD1 agents, has confirmation of EGFR, ALK, ROS1, BRAF, NTRK, MET, and RET mutations that are negative or unknown, and individual has had no prior platinum-doublet chemotherapy. At this time, there is insufficient evidence to support such use.

The NCCN also provides a category 2A recommendation for use in thymic cancer and thymomas as first-line therapy when preferred first-line combination regimens are not tolerated. At this time, there is insufficient data to support such use.

The NCCN CPGs in Oncology for primary CNS lymphoma include a recommendation for the use of pemetrexed in the treatment of recurrent or progressive primary CNS lymphoma. The 2A recommendation is based on a single study conducted by Raizer and colleagues (2012) which enrolled 11 participants with relapsed/refractory PCNSL to assess for single agent activity based on OS, PFS and response rates. Ten of the 11 participants had previously been treated with high-dose methotrexate. The 6-month PFS was 45%, median PFS was 5.7 months and median OS was 10.1 months. Toxicities experienced were largely infectious and hematologic. Authors conclude that pemetrexed demonstrated single-agent activity in relapsed/refractory PCNSL. At this time, the published data does not demonstrate the efficacy of pemetrexed in the treatment of PCNSL.

NCCN CPG for mesothelioma also includes a 2A recommendation for pemetrexed-based chemotherapy for unresectable malignant peritoneal mesothelioma or tunica vaginalis testis mesothelioma, relatively rarer forms of mesothelioma. Evidence for peritoneal mesothelioma, which accounts for about 30% of mesothelioma cases, consists of results from two open-label, expanded-access programs that found pemetrexed safe and active for this indication (Carteni, 2009; Jänne, 2005). To date, there are no published studies on pemetrexed's efficacy in tunica vaginalis testis which accounts for less than 1% of mesothelioma cases, though NCCN endorses it as a reasonable treatment approach for unresectable disease based on expert consensus.

Definitions and Measures

Chemotherapy: Medical treatment of a disease, particularly cancer, with drugs or other chemicals.

ECOG or Eastern Cooperative Oncology Group Performance Status: A scale and criteria used by doctors and researchers to assess how an individual's disease is progressing, assess how the disease affects the daily living abilities of the individual, and determine appropriate treatment and prognosis. This scale may also be referred to as the WHO (World Health Organization) or Zubrod score which is based on the following scale:

- 0 = Fully active, able to carry on all pre-disease performance without restriction
- 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
- 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- 5 = Dead

Immune checkpoint inhibitor: A type of drug that blocks certain proteins made by some types of immune system cells, such as T cells, and some cancer cells. When these proteins are blocked, the "brakes" on the immune system are released and T cells are able to kill cancer cells better. Examples of checkpoint proteins found on T cells or cancer cells include programmed death (PD)-1, PD-ligand 1 (PD-L1), and cytotoxic T-lymphocyte–associated antigen (CTLA)-4/B7-1/B7-2.

Line of Therapy:

- First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
- Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
- Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second-line therapy) are not effective or there is disease progression.

Maintenance therapy: Designed to maintain a condition to prevent a relapse.

Metastasis: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.

Non-small cell lung cancer: A group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of non-small cell lung cancer are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma.

Programmed death (PD)-1 proteins: PD-1 proteins are found on T-cells and attach to PD ligands (PD-L1) found on normal (and cancer) cells (see immune checkpoint inhibitor above). Normally, this process keeps T-cells from attacking other cells in the body. However, this can also prevent T-cells from attacking cancer cells in the body. Examples of FDA approved anti-PD-1 agents include Keytruda (pembrolizumab), Opdivo (nivolumab), and Libtayo (cemiplimab).

Programmed death ligand (PD-L)-1: The ligands found on normal (and cancer) cells to which the PD-1 proteins attach (see immune checkpoint inhibitor above). Cancer cells can have large amounts of PD-L1 on their surface, which helps them to avoid immune attacks. Examples of FDA approved anti-PD-L1 agents include Bavencio (avelumab), Tecentriq (atezolizumab), and Imfinzi (durvalumab).

Refractory Disease: Illness or disease that does not respond to treatment.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Pemetrexed Agents (Alimta, Pemfexy)

Requests for Pemetrexed Agents (Alimta, Pemfexy) may be approved if the following criteria are met:

I. Individual has a diagnosis of malignant mesothelioma; **AND**
   A. Individual is using in combination with cisplatin or carboplatin (Label, NCCN 2A);

   OR
   B. Individual is using as a first-line therapy in combination with cisplatin or carboplatin AND bevacizumab (or bevacizumab biosimilar) (Label, NCCN 2A); **AND**
      1. Individual has an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; **AND**
      2. Individual does not have a history of hemoptysis or thrombosis; **AND**
      3. Disease presentation is unresectable;

   OR
   C. Individual is using as single agent for subsequent therapy (NCCN 1); **AND**
      1. Pemetrexed was not administered as first-line; **OR**
      2. Pemetrexed was used as first-line with good sustained response;

OR

II. Individual has a diagnosis of recurrent, locally advanced, or metastatic non-squamous, non-small cell lung cancer (NSCLC); **AND**
   A. Individual is using as a single agent after prior chemotherapy; **OR**
   B. Individual is using as a first-line therapy in combination with platinum based chemotherapy with or without bevacizumab (or bevacizumab biosimilar) (NCCN 2A); **OR**
   C. Individual is using as second-line therapy (first-line chemotherapy) in combination with platinum-based chemotherapy with or without bevacizumab (or bevacizumab biosimilar) if tyrosine-kinase inhibitor (TKI/anaplastic lymphoma kinase (ALK) targeted agent was given as first-line therapy (NCCN 1) ; **OR**
   D. Individual is using for maintenance therapy when disease has not progressed following four cycles of platinum-based, first-line therapy; **OR**
   E. Individual is using in combination with pembrolizumab (Keytruda) and platinum chemotherapy for initial treatment and without presence of actionable molecular markers* (Label, NCCN 2A); **OR**
   F. Individual is using as continuous maintenance therapy until disease progression, if given first-line as part of Keytruda (pembrolizumab)/platinum chemotherapy/and pemetrexed regimen (NCCN 1); **OR**
   G. Individual is using as first-line therapy in combination with nivolumab, ipilimumab, *and* platinum-based chemotherapy and without presence of actionable molecular markers* (NCCN 2A); **OR**
   H. Individual is using as adjuvant or neoadjuvant therapy in combination with platinum-based chemotherapy;

OR

III. Individual is using as a single-agent therapy; **AND**
IV. Individual has one of the following (NCCN 2A):
   A. Individual has a diagnosis for persistent or recurrent ovarian cancer; **OR**
   B. Individual has a diagnosis for thymic cancer and thymomas and using as second-line therapy and beyond.

***Note:** Actionable molecular markers include EGFR, ALK, ROS1, BRAF, NTRK, MET and RET mutations. The NCCN panel recommends testing prior to initiating therapy to help guide appropriate treatment. If there is insufficient tissue to allow testing for all of these markers, 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 (NCCN 2A).

Requests for Pemetrexed Agents (Alimta, Pemfexy) may not be approved for the following:

I. Individual has a diagnosis of squamous cell non-small cell lung cancer; **OR**
II. When the above criteria are not met and for all other indications.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J9304	Injection, pemetrexed, 10 mg [Pemfexy]
J9305	Injection, pemetrexed, NOS, 10 mg [Alimta]

ICD-10 Diagnosis

C34.00-C34.92	Malignant neoplasm of bronchus and lung
C37	Malignant neoplasm of thymus
C38.0-C38.8	Malignant neoplasm of heart, mediastinum and pleura
C45.0-C45.9	Mesothelioma
C48.0-C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C56.1-C56.9	Malignant neoplasm of ovary
C57.00-C57.9	Malignant neoplasm of other and unspecified female genital organs
C61	Malignant neoplasm of prostate
C65.1-C65.9	malignant neoplasm of renal pelvis
C66.1-C68.0	Malignant neoplasm of ureter, bladder, urethra
C78.00-C78.02	Secondary malignant neoplasm of lung
C78.2	Secondary malignant neoplasm of pleura
D15.0	Benign neoplasm of thymus
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
Z85.238	Personal history of other malignant neoplasm of thymus

Document History

Reviewed: 02/25/2022
Document History:

- 02/25/2022 – Annual Review: No changes. Coding Reviewed: No changes.
- 02/19/2021 – Annual Review: Update criteria to add new agent Pemfexy (pemetrexed) to document. Update NSCLC criteria to allow use in recurrent disease, and add use in combination with nivolumab, ipilimumab, *and* platinum-based chemotherapy per guidelines. Update NSCLC criteria to specify any actionable molecular marker with a note to further expand on definition and marker testing. Add indication for use as adjuvant or neoadjuvant therapy in NSCLC. Wording and formatting updates. Coding Reviewed: Added J9304.
- 08/21/2020 – Select Review: Update criteria for first line use in NSCLC with Keytruda in individuals with negative or unknown EGFR, ALK, ROS1, and BRAF mutations. Coding Reviewed: No changes.
- 02/21/2020 – Annual Review: Update criteria to add use in malignant mesothelioma as single agent, subsequent therapy per NCCN recommendations. Update approvable criteria to remove use in urothelial carcinoma per NCCN update. Update non-approvable criteria for consistency. Add notation in criteria for interchangeability with bevacizumab biosimilar for mesothelioma and NSCLC indications. Wording and formatting changes. Coding Reviewed: Added ICD-10-CM C37, C45.0-C45.9, C56.1-C56.9

- 08/16/2019 – Select Review: Wording and formatting changes for clarity.
- 05/17/2019 – Annual Review: First review of Alimta (pemetrexed). Update Alimta criteria for consistency to include FDA label update for use in combination with pembrolizumab (Keytruda) and platinum chemotherapy for metastatic non-squamous NSCLC as initial treatment in those without EGFR or ALK genomic tumor aberrations. Update Alimta criteria for consistency to include NCCN recommendations for combination use of Alimta with or without bevacizumab in non-squamous NSCLC. Wording and formatting changes. Coding reviewed: Revised code: No change.

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    a. Central Nervous System Cancers. V2.2021. Revised September 8, 2021.
    b. Malignant Pleural Mesothelioma. V1.2022. Revised December 22, 2021.
    c. Non-Small Cell Lung Cancer. V1.2022. Revised December 7, 2021.
    d. Ovarian Cancer, including fallopian tube cancer and primary peritoneal cancer. V3.2021. Revised September 9, 2021.
    e. Thymomas and Thymic Carcinomas. V1.2022. Revised December 22, 2021.
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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.