Name of Policy:
Alimta® (pemetrexed disodium)

Policy #: 652  
Category: Pharmacology

Latest Review Date: March 2016  
Policy Grade: A

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
Description of Procedure or Service:
Alimta® (pemetrexed) is a folate analog metabolic inhibitor that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication. In vitro studies have shown that pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is taken into cells by membrane carriers such as the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are inhibitors of TS and GARFT. Polyglutamation is a time- and concentration-dependent process that occurs in tumor cells and, is thought to occur to a lesser extent, in normal tissues. Polyglutamated metabolites are thought to have an increased intracellular half-life resulting in prolonged drug action in malignant cells.

Requirement for Premedication and Concomitant Medication to Reduce Toxicity
Vitamin Supplementation
Prior to treatment with Alimta, initiate supplementation with oral folic acid and intramuscular vitamin B12 to reduce the severity of hematologic and gastrointestinal toxicity of Alimta. Do not substitute oral vitamin B for intramuscular vitamin B12. In clinical studies, the incidence of the following Grade 3-4 toxicities were higher in patients with mesothelioma who were never supplemented as compared to patients who were fully supplemented with folic acid and vitamin B12 prior to and throughout Alimta treatment: neutropenia [38% versus 23%], thrombocytopenia [9% versus 5%], febrile neutropenia [9% versus 0.6%], and infection with neutropenia [6% versus. 0].

Corticosteroids
Administer dexamethasone 4 mg by mouth twice daily the day before, the day of, and the day after Alimta administration.

Policy:
Alimta (pemetrexed disodium heptahydrate) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for treatment of locally advanced or metastatic stage (III-IV) nonsquamous non-small cell lung cancer for any one of the following indications:
- Used in combination with cisplatin or carboplatin with radiation therapy for definitive treatment, OR
- Used in combination with cisplatin or carboplatin for first-line chemotherapy, OR
- Used for maintenance therapy when disease has not progressed following 4 cycles of platinum- based first-line chemotherapy (regardless of whether pemetrexed [Alimta] was used in combination with the platinum based first-line chemotherapy), OR
- Used after prior chemotherapy as a single agent

Alimta (pemetrexed disodium heptahydrate) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage of non-small cell lung cancer when used as adjuvant or induction therapy in combination with cisplatin (or carboplatin if contraindicated).
**Alimta (pemetrexed disodium heptahydrate) meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for treatment of **malignant pleural mesothelioma** for ANY one of the following indications:

- Used in combination with cisplatin or carboplatin (with or without bevacizumab for unresectable disease) for first-line chemotherapy, OR
- Used as a single agent for second-line chemotherapy

**Alimta (pemetrexed disodium heptahydrate) meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for treatment of **metastatic bladder cancer** or **metastatic urothelial carcinoma** as a single agent for second-line or greater.

**Alimta (pemetrexed disodium heptahydrate) meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for treatment of **recurrent ovarian cancer** as a single agent in platinum resistant disease.

**Alimta (pemetrexed disodium heptahydrate) meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for another FDA labeled indication or an NCCN 1 or 2A recommended indication and the requested dose and duration is within the FDA labeling or NCCN 1 or 2A compendia supported dosing.

*Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

**Key Points:**

**Nonsquamous Non-Small Cell Lung Cancer**

It is estimated that in the U.S. there are between 221,200-225,000 new cases of lung cancer annually. Approximately 95% of lung cancers are either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC). Patients with stage I, II, or III non-small cell lung cancer (NSCLC) are generally treated with curative intent using surgery, chemotherapy, radiation therapy (RT), or a combined modality approach. Only approximately 16.8% of all patients with lung cancer are alive 5 years or more after diagnosis. When there is a solitary metastasis, surgical resection or radiation therapy are two appropriate treatment options. When there is advanced disease (stage IV/those that present with metastases or there is recurrence after initial treatment), systemic therapy is typically utilized. Upon progression to advanced disease, the intent tends to shift from a curative intent to a more palliative intent.

Pemetrexed was analyzed in 3 trials involving NSCLC: 1) in combination with cisplatin, 2) as maintenance therapy following non-Alimta containing platinum-based induction therapy, 3)
continuation of Alimta maintenance therapy following Alimta induction therapy, and 4) after prior chemotherapy vs docetaxel.

NSCLC - In Combination with Cisplatin (first-line therapy)
A multi-center, randomized, open label study in 1725 chemonaive patients who had Stage IIIb/IV NSCLC was conducted to compare the overall survival following treatment with Alimta + cisplatin (N=862) vs gemcitabine + cisplatin (N=863). Up to 6 cycles were administered and both treatment arms also received folic acid, vitamin B12, and dexamethasone. The median overall survival time was the same in both the Alimta + cisplatin group and the Gemcitabine + cisplatin group at 10.3 months with the median progression-free survival at 4.8 months and 5.1 months respectively. There was a lack of efficacy found in patients with squamous cell histology.

NSCLC- Maintenance Following Non-Alimta Containing Platinum-based Induction Therapy
A multi-center, randomized, double-blind, placebo-controlled study was conducted in 663 patients who had Stage IIIb/IV NSCLC who did not progress after receiving 4 cycles of platinum-based chemotherapy. Patients were randomized 2:1 to either receive Alimta (N=441) or placebo (N=222) immediately following platinum-based chemotherapy. Alimta was administered until disease progression (500 mg/m2 on day 1 of every 21-day cycle). Both study arms also received folic acid, vitamin B12, and dexamethasone. The study was designed to show superior progression-free survival and overall survival with Alimta over placebo. In the overall study population, Alimta was statistically superior to placebo in terms of overall survival (OS) (median 13.4 months versus 10.6 months, HR=0.79 (95% CI: 0.65-0.95), p-value=0.012) and PFS (median 4.0 months versus 2.0 months, HR=0.60 (95% CI: 0.49-0.73), p-value<0.00001). Similar to the study where Alimta was used first-line in combination with cisplatin, the patients with squamous NSCLC did not have an improvement in overall survival compared to placebo (median 9.9 months versus 10.8 months, HR=1.07 [95% CI: 0.77-1.50]) or progression-free survival compared to placebo (median 2.4 months versus 2.5 months, HR=1.03 [95% CI: 0.71-1.49]).

NSCLC- Continuation of Alimta as Maintenance Following Alimta plus Platinum Induction Therapy
A multi-center, randomized, double-blind, placebo-controlled study was conducted to evaluate continuation of Alimta therapy in patients with Stage IIIb/IV nonsquamous NSCLC. All patients in the study completed 4 cycles of Alimta + cisplatin (and had to have stable disease or better after the 4 cycles) and were then randomized (2:1) to either maintenance Alimta therapy (N=359) or placebo (N=180). Randomization was stratified by response to induction (complete response (CR)/partial response (PR) versus stable disease (SD)), disease stage (IIIb versus IV), and ECOG performance status (0 versus 1). Similar to the other two studies conducted, all patients also received folic acid, vitamin B12, and dexamethasone. The trial showed a statistically significant improvement in progression-free survival and in overall survival for patients on Alimta maintenance therapy. The median overall survival was 13.9 vs 11.0 months in Alimta vs placebo respectively (95% CI; Hazard ratio 0.78, p-value= 0.02) and median progression-free survival was 4.1 months vs 2.8 months respectively (95% CI, HR 0.62, p<0.0001).
NSCLC - After Prior Chemotherapy: Alimta vs Docetaxel
A multi-center, randomized, open label study was conducted to show overall survival superiority or non-inferiority of Alimta (N=283) to docetaxel (N=288) in Stage III/IV NSCLC patients who received prior chemotherapy. Those receiving Alimta also received folic acid and vitamin B12. The study did not show an overall survival superiority of Alimta. The median overall survival was 8.3 months for Alimta and 7.9 months for docetaxel (95% CI; HR 0.99), median progression-free survival was 2.9 months for both (95% CI, 0.97), and the overall response rate was 8.5% for Alimta and 8.3% for docetaxel (95% CI). In a retrospective analysis, it was found that Alimta was not effective in squamous cell histology.

Malignant Pleural Mesothelioma:
Mesothelioma is a neoplasm that starts in the mesothelial surfaces of the pleural and peritoneal cavities, the tunica vaginalis, or the pericardium. It is a rare cancer that is estimated to occur in approximately 2,500 patients in the U.S. annually. Pleural mesothelioma is the dominant form and is estimated to be approximately 80% of mesothelioma cases. More often than not, malignant mesothelioma is caused by inhalation of asbestos (approximately 70% of cases). There are reports and recent data that suggest that ionizing radiation and erionite (a mineral that may be found in gravel roads) may also cause mesothelioma. Clinically, patients have a gradual onset of pulmonary symptoms (very nondescript symptoms such as chest pain, dyspnea, cough) that often do not present until advanced disease. Typically its morbidity/mortality is caused by gradual local invasion of the pleural space eventually causing fatigue, dyspnea, and hypoxemia that is often not responsive to supplemental oxygen. Historically, malignant mesothelioma has been associated with a very poor prognosis with a median survival of 6 months-1 year; cure is rare.

Pemetrexed was analyzed in 1 trial involving malignant pleural mesothelioma (MPM). A multi-center, randomized, single-blind study was conducted in 448 chemonaive patients with MPM comparing survival in patients that either received Alimta + cisplatin (N=226) or cisplatin alone (N=222). The median overall survival for Alimta + cisplatin was 12.1 months vs 9.3 months on cisplatin alone (95% CI; HR 0.77; p=0.020). After 117 patients were treated in the trial, there was a change in protocol and all patients received folic acid and vitamin B12 supplementation due to white cell and gastrointestinal toxicity (versus only a selected amount of patients received vitamin supplementation and the rest did not). Those who received vitamin supplementation from the time of enrollment in the trial fared better in median overall survival. Alimta + cisplatin patients had a median overall survival of 13.3 months and the cisplatin patients had a median overall survival of 10.0 months (95% CI; HR 0.75; p=0.051).

Key Words:
Non-small cell lung cancer (NSCLC), nonsquamous non-small cell lung cancer, malignant pleural mesothelioma, metastatic bladder cancer, urothelial carcinoma, ovarian cancer, Alimta, pemetrexed
**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

**Current Coding:**
CPT Codes:

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<thead>
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<th>Code</th>
<th>Description</th>
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<tr>
<td>J9305</td>
<td>Injection, pemetrexed, 10 mg</td>
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**References:**
10. UpToDate. Epidemiology of malignant pleural mesothelioma.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.