



**BlueCross BlueShield
of Alabama**

Name of Policy:

Alimta® (pemetrexed disodium)

Policy #: 652
Category: Pharmacology

Effective Date: April 16, 2018
Last Review Date: March 2018

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 glycylamide 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.

Policy:

Effective for dates of service on or after April 16, 2018

Alimta® (pemetrexed disodium) 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 (NSCLC) for any one of the following indications:

- Used as first-line therapy in combination with cisplatin or carboplatin; **OR**
- Used as a single agent after prior chemotherapy; **OR**
- Used in combination with cisplatin or carboplatin with radiation therapy for definitive treatment; **OR**
- Used in combination with cisplatin or carboplatin for subsequent therapy for sensitizing EGFR mutation-positive tumors following erlotinib, afatinib, gefitinib, or osimertinib therapy; **OR**
- Used in combination and cisplatin or carboplatin for subsequent therapy for ALK positive tumors following crizotinib, ceritinib, alectinib, or brigatinib therapy; **OR**
- Used in combination with cisplatin or carboplatin for subsequent therapy for ROS1 positive tumors following crizotinib or ceritinib therapy; **OR**
- Used in combination with cisplatin or carboplatin for subsequent therapy for BRAF V600E positive tumors

Alimta® (pemetrexed disodium) meets Blue Cross and Blue Shield of Alabama's criteria for coverage as **maintenance therapy for **locally advanced or metastatic non-squamous NSCLC** when disease has not progressed following four cycles of platinum-based, first-line therapy.**

Alimta® (pemetrexed disodium) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage of **non-squamous non-small cell lung cancer when used as adjuvant or induction therapy in combination with cisplatin (or carboplatin if contraindicated).**

Alimta® (pemetrexed disodium) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for treatment of **unresectable malignant pleural mesothelioma** for **ANY** one of the following indications:

- Used as a single agent or combination therapy with cisplatin or carboplatin; OR
- Used in combination with bevacizumab and cisplatin or carboplatin for individuals with performance status of 0-1 and no history of hemoptysis or thrombosis; OR
- Used as a single agent for second line chemotherapy, if not administered first line

Alimta® (pemetrexed disodium) 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) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for treatment of **ovarian cancer** as a single agent for persistent disease or recurrence.

Alimta® (pemetrexed disodium) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for treatment of **thymic cancer and thymomas** when used for second line therapy as a single agent.

When medical necessity criteria are met for **Alimta® (pemetrexed disodium)** the following laboratory studies must be monitored routinely for ANC, platelets and creatinine clearance, including at the beginning of each cycle; the drug should **not** be given when:

- ANC < 1500 cells/mm³
- Platelets < 100,000
- Creatinine clearance < 45ml/min

Alimta (pemetrexed disodium) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** when the above criteria are not met and for all other indications, including but not limited to, primary central nervous system lymphoma, or squamous cell non-small cell lung cancer.

Effective for dates of service February 24, 2017 through March 1, 2018

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 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; OR**
- **Used in combination with cisplatin or carboplatin with radiation therapy for definitive treatment; OR**
- **Used in combination with cisplatin or carboplatin for subsequent therapy for sensitizing EGFR mutation-positive tumors following erlotinib, afatinib, or gefitinib therapy.**

- Used in combination with cisplatin or carboplatin for subsequent therapy for ALK positive tumors following crizotinib therapy.

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 **unresectable 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 treatment of **thymic cancer and thymomas** when used for second line therapy as a single agent.

Alimta (pemetrexed disodium heptahydrate) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** when the above criteria is not met.

Effective for dates of service May 1, 2016 through February 23, 2017

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.

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:

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, and 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.

In 2003, Vogelzang and colleagues conducted a randomized, single-blind, multi-center, phase III trial to evaluate the efficacy and safety of pemetrexed combined with cisplatin versus single-agent cisplatin. Overall survival (OS) was the primary endpoint of interest in this clinical trial. A total of 448 individuals were enrolled and randomized into either the pemetrexed+cisplatin arm

(n=226) or the cisplatin-only arm (n=222). Median OS times were 12.1 months and 9.3 months for the pemetrexed+cisplatin and cisplatin-only arms, respectively (p=0.020). After the first 117 participants, folic acid and vitamin B12 were added to reduce toxicities; a significant reduction in toxicities was seen in the pemetrexed+cisplatin arm. Authors concluded that treatment with pemetrexed and cisplatin with vitamin supplementation achieved superior response rates, time to progression (TTP) and survival time. FDA approval was based on the results of this study demonstrating superior survival as a clinical benefit of pemetrexed+cisplatin in the treatment of malignant pleural mesothelioma when compared to cisplatin alone.

The National Comprehensive Cancer Network (NCCN®) Clinical Practice Guidelines (CPGs) in Oncology® for malignant pleural mesothelioma include a 2A recommendation for use of carboplatin in combination with pemetrexed for the treatment of mesothelioma. In 2008, Santoro and colleagues published results of the International Expanded Access Program on the efficacy and safety of pemetrexed+cisplatin (PemC) versus pemetrexed+carboplatin (PemCar) as a first-line of therapy in malignant pleural mesothelioma. A total of 1704 participants were enrolled in this open-label, nonrandomized clinical trial; n=843 in the PemC arm and n=861 in the PemCar arm. The overall response rate (ORR), TTP, 1-year survival rates and toxicities were similar between both arms. Authors concluded that cisplatin and carboplatin demonstrate similar efficacy and safety as a component of a pemetrexed-based chemotherapy regimen in the treatment of malignant pleural mesothelioma.

The NCCN CPG (2018) includes a 2A off-label recommendation for use of pemetrexed as first-line combination chemotherapy with bevacizumab and cisplatin for the treatment of unresectable malignant pleural mesothelioma. The evidence cited with this category 2A recommendation includes published data from a multicenter, phase III, randomized, clinical trial. A total of 448 participants aged 18-75 years with unresectable malignant pleural mesothelioma who were chemotherapy naïve, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, no substantial cardiovascular comorbidity, were not amenable to curative surgery, had at least one evaluable (pleural effusion) or measurable (pleural tumor solid thickening) lesion confirmed by computerized tomography scan, and a life expectancy of at least 12 weeks, were randomly allocated 1:1 to receive pemetrexed+cisplatin (n=225 [PC]) or PC+bevacizumab (n=233 [PCB]) for up to six cycles, until progression or toxic effects. For grade 2 or higher cisplatin-induced renal toxic effects, participants were allowed a switch to carboplatin. The primary outcome was OS in the intention-to treat population. OS was reported as significantly extended in the PCB arm (median OS 18.8 months [95% CI, 15.9-22.6]; 164 of 223 [74%] died) than in the PC arm (median OS 16.1 months [14.0-17.9]; 178 of 225 [79%] died; Hazard Ratio [HR] 0.77 [0.62-0.95]; p=0.0167). PFS was also significantly improved with PCB (median PFS 9.2 months [8.5-10.5]; 198 of 223 [89%] died) compared to the PC arm (7.3 months [6.7-8.0]; 217 of 225 [96%] died; adjusted-HR 0.61 [0.50-0.75]; p<0.0001). More participants stopped first-line treatment for disease progression in the PC arm (189 [87.1%] of 217) than in the PCB arm (137 [62.8%] of 218; difference 24.3% [16.3-31.9]; p<0.0001). Grade 3-4 adverse events were reported in 158 (71%) of 222 participants in the PCB arm and 139 (62%) of 224 participants in the PC arm. Non-hematological adverse events in both groups included asthenia or fatigue, anorexia, constipation, and nausea or vomiting. There were more grade 3 or higher hypertension (51 [23%] of 222 vs. 0) and thrombotic events (13 [6%] of 222 vs. 2 [1%] of 224) in the PCB arm than in the PC arm. Limitations of this trial include the open-label design. Based

on the 2.7 month OS improvement rate reported in this large, multicenter, phase III, randomized trial, the NCCN (category 2A) considers combination therapy with pemetrexed, cisplatin, and bevacizumab an acceptable chemotherapy regimen for individuals with unresectable malignant pleural mesothelioma.

NCCN CPGs for mesothelioma (2018) also include 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. 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.

Pemetrexed was analyzed in 1 trial involving malignant pleural mesothelioma (MPM). A multicenter, randomized, single-blind study was conducted in 448 chemonaïve 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).

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.

In 2004, Hanna and colleagues conducted a non-blinded, randomized phase III trial to examine efficacy and toxicity of pemetrexed versus docetaxel in the treatment of advanced or metastatic NSCLC. A total of 571 participants were randomly assigned to 1 of the 2 treatment arms. Eligible participants had a performance status of 2 or better, previous chemotherapy treatment regimen for NSCLC, and satisfactory organ function. Once enrolled, the remaining 541 participants (30 participants dropped out, 18 and 12 from the pemetrexed and docetaxel arms, respectively, for a variety of unrelated reasons) either received 500 mg/m² of pemetrexed on day 1 with vitamin B12, folic acid and dexamethasone (n=265), or standard treatment of docetaxel 75

mg/m² on day 1 with dexamethasone (n=266). The primary outcome of interest was overall survival (OS). Overall response rate (ORR) was 9.1% and 8.8% for pemetrexed and docetaxel, respectively (not statistically significant). Median progression-free survival (PFS) was 2.9 months in each arm and median OS was 8.3 months versus 7.9 months for pemetrexed and docetaxel, respectively (not statistically significant). In this large, randomized controlled trial, authors concluded that pemetrexed treatment provided equivalent clinical efficacy to docetaxel but side effects, such as grade 3 or 4 neutropenia, febrile neutropenia and hospitalizations, were significantly reduced with pemetrexed. Initial FDA approval for the treatment of NSCLC with pemetrexed was based on this trial. A recent meta-analysis of four randomized controlled trials, representing 1084 participants, confirmed that pemetrexed, single-agent, remains the safest and most efficacious approach after prior chemotherapy, compared to treatment with a platinum-based doublet.

In 2007, a retrospective study was performed by Peterson and colleagues examining the histology of the previously described randomized phase III trial which determined the OS rates of pemetrexed versus docetaxel in the treatment of advanced or metastatic NSCLC were comparable. Peterson's investigation identified a statistically significant treatment-by-histology interaction (p=0.001); those with squamous cell NSCLC had significantly better survival when treated with docetaxel rather than pemetrexed (p=0.018). For the non-squamous sub-group, pemetrexed was statistically superior to docetaxel (p=0.048). Based on the results of this study, the FDA revised its approval of pemetrexed treatment to include only non-squamous histology of NSCLC.

Scagliotti and colleagues conducted a multi-center, randomized phase III, open-label study of pemetrexed with cisplatin (AC) versus gemcitabine plus cisplatin (GC) in chemotherapy-naïve individuals diagnosed with stage IIIB/IV non-squamous NSCLC. A total of 1725 individuals were enrolled and randomly assigned to either the AC (n=862) or GC (n=863) arm. The primary outcome of interest was OS. Median OS was 10.3 months in both the AC and GC arm (adjusted HR not statistically significant) and median PFS times were 4.8 months and 5.1 months for the AC and GC arms, respectively (HR not statistically significant). Although noninferiority could not be conclusively demonstrated, the FDA's opinion was that there is substantial evidence that pemetrexed is sufficiently active as a first-line treatment in non-squamous NSCLC and in 2008 it was approved for use in combination with cisplatin for this indication.

A systematic review and meta-analysis was published by Xiao and colleagues on the efficacy of pemetrexed plus platinum doublet chemotherapy as first-line treatment for advanced non-squamous NSCLC. A total of 2551 individuals were enrolled from 10 clinical trials, 1565 of which had received pemetrexed as first-line treatment with a platinum-based doublet and the remaining 986 received a chemotherapy other than pemetrexed with a platinum doublet as a first-line of treatment. Pooled OS was significantly longer in those treated with pemetrexed and a platinum doublet versus another chemotherapy and a platinum doublet (p=0.01), further confirming the efficacy and safety of this regimen in advanced non-squamous NSCLC.

Langer and colleagues (2016) conducted the phase I/II KEYNOTE-021 trial, an open-label, multicenter, multi-cohort study that evaluated tumor response and progression-free survival in individuals with nonsquamous NSCLC. Individuals with chemotherapy-naïve, stage IIIB or IV,

non-squamous NSCLC were randomly assigned (1:1) to receive pemetrexed every 3 weeks followed by pembrolizumab for 24 months and indefinite pemetrexed maintenance therapy or to 4 cycles of carboplatin and pemetrexed alone followed by indefinite pemetrexed maintenance therapy. The primary endpoint was the proportion who achieved an objective response (percentage of patients with radiologically confirmed complete or partial response). A total of 123 individuals were enrolled; 60 were randomly assigned to the pembrolizumab plus chemotherapy group and 63 to the chemotherapy alone group. At the time of analysis, 33 (55%; 95% CI, 42-68) of 60 study participants in the pembrolizumab plus chemotherapy group achieved an objective response compared with 18 (29%; 18-41) of 63 study participants in the chemotherapy alone group (estimated treatment difference 26% [95% CI, 9-42%]; p=0.0016). The incidence of grade 3 or worse treatment-related adverse events was similar between the two groups. The NCCN has given a category 2A recommendation for the combination treatment of NSCLC with pemetrexed, a platinum-based therapy and pembrolizumab. This combination therapy regimen is continuing to be investigated in a phase III, manufacture-sponsored clinical trial.

Both the NCCN CPGs in Oncology for NSCLC (2018) and the American Society of Clinical Oncology (ASCO) guidelines on 'Systemic Therapy for Stage IV NSCLC' recommend treatment with pemetrexed for second-line of therapy in combination with platinum-based chemotherapy if a tyrosine-kinase inhibitor (TKI)/targeted agent was given as first-line therapy. The recommendations are based on consensus but considered appropriate in the less conventional treatment approach necessitated by sensitizing epidermal growth factor receptor (EGFR) mutations.

Non-Small Cell Lung Cancer Maintenance Therapy

In 2009, Ciuleanu and colleagues published results of a randomized, double-blind phase III study to assess the efficacy and safety of pemetrexed with best supportive care (BSC) compared to placebo with BSC in individuals with locally advanced or metastatic NSCLC whose disease had not progressed following four cycles of platinum-based, doublet induction chemotherapy. OS was the primary outcome of interest. In total, 663 participants were randomized into 1 of each arms (pemetrexed, n=441; placebo, n=222). The median OS in the treatment arm was 15.5 months versus 10.3 months in the placebo arm for those participants with non-squamous cell histology (HR=0.70; 95% confidence interval [CI], 0.65-0.88). Based on the superior outcome of the pemetrexed arm in non-squamous cell NSCLC participants, the FDA approved pemetrexed for use in maintenance treatment of this population when their disease has not progressed after four cycles of platinum-based doublet induction therapy. Paz-Ares replicated the study design in another randomized, double-blind phase III study of 939 individuals. Randomization was 2:1 in the pemetrexed+BSC arm (n=359) and placebo+BSC arm (n=180), respectively. Similarly, pemetrexed treatment was found superior to BSC based on OS of 13.9 months versus 11.0 months in the non-treatment arm (HR=0.78, 95% CI, 0.64-0.96; p=0.0195). The treatment regimen was relatively well tolerated and authors conclude that the study findings further support the efficacy and safety of pemetrexed as a single-agent maintenance therapy in advanced non-squamous NSCLC. Long-term study results continue to affirm these findings.

The NCCN CPGs in Oncology for NSCLC include a 2A recommendation for the use of 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. In 2009, Patel and colleagues conducted a nonrandomized, phase II trial evaluating the safety and efficacy of cisplatin, pemetrexed and bevacizumab in chemotherapy-naïve, advanced non-squamous NSCLC. Pemetrexed and bevacizumab therapy were continued until treatment failure occurred; 60% received greater than 6 cycles. In total, 49 participants were enrolled and available for evaluation; 55% experienced an objective response. PFS and OS were 7.8 months and 14.1 months, respectively. Incidence of grade 3-4 toxicities were modest and based on the findings of this study, a Phase III trial was recommended. In 2013, Patel and colleagues reported findings from a randomized, open-label, phase III trial evaluating the safety and efficacy of induction therapy with carboplatin, pemetrexed and bevacizumab, followed by maintenance with pemetrexed plus bevacizumab (PemCBev) versus paclitaxel, carboplatin and bevacizumab, followed by bevacizumab alone (PacCBev; standard of care for first-line therapy), in advanced non-squamous NSCLC. The primary endpoint was OS; secondary endpoints included PFS, ORR, disease control rate (partial response [PR] + complete response [CR] + stable disease), TTP and toxicities. In total, 939 participants were enrolled and randomized, 1:1 to the PemCBev arm (n=472) or the PacCBev arm (n=467); 292 and 298 participants were eligible for and received maintenance therapy with PemCBev and PacCBev, respectively. OS and survival at 12 and 24 months was not statistically different between the PemCBev and PacCBev arms in this study. Secondary endpoints of PFS (6.0 vs 5.6 months; HR=0.83, 95% CI, 0.71-0.96; p=0.012) and TTP (7.0 vs 6.0 months; HR=0.79, 95% CI, 0.67 to 0.94; p=0.006) were significantly better in the PemCBev arm. Grade 3-4 toxicities of neutropenia, alopecia and neuropathy were significantly lower in the PemCBev arm while thrombocytopenia, anemia and fatigue were lower in the PacCBev arm. The trial's primary endpoint was not met, but authors concluded that the treatment options explored in this trial were comparably safe and efficacious as induction and maintenance therapies in advanced NSCLC.

Similarly, Barlesi and colleagues conducted a randomized, open-label, phase III trial evaluating the safety and efficacy of maintenance therapy with pemetrexed, with and without bevacizumab in advanced non-squamous NSCLC. In total, 376 individuals were enrolled and received four cycles of induction therapy with pemetrexed, cisplatin and bevacizumab. The study's primary endpoint was PFS. If a CR, PR or stable disease (SD) was achieved (n=253; 72%), participants were randomized 1:1 to receive bevacizumab (n=125) or bevacizumab+pemetrexed (n=128) as maintenance therapy. Investigators found that bevacizumab+pemetrexed (7.4 months) achieved a superior PFS to bevacizumab alone (3.7 months) as maintenance therapy (HR=0.48, 95% CI, 0.35-0.66; p=0.001). Investigators conclude from this trial's results that bevacizumab+pemetrexed demonstrated improved clinical benefit when compared to bevacizumab alone in the maintenance treatment of advanced NSCLC in those who had achieved disease control with pemetrexed, cisplatin and bevacizumab. Barlesi and colleagues continued this investigation in a subsequent publication evaluating overall survival in this same clinical trial cohort and found that after a median follow-up of 14.8 months from randomization, individuals in the bevacizumab+pemetrexed arm continued to have statistically longer PFS; however, 1-year and 2-year OS differences did not reach statistical significance. There was an increase in grade 3 and 4 adverse events in the bevacizumab+pemetrexed arm, and a separately published study from the same cohort noted that health-related quality of life (HRQOL) was not improved in the combination bevacizumab+pemetrexed arm. An additional, smaller clinical trial (n=110) also investigated maintenance bevacizumab+pemetrexed versus pemetrexed alone in

non-squamous NSCLC and similarly found no differences in the superiority of PFS between these treatments and increased adverse events with the combination therapy. Consequently, there is a lack of evidence in the peer-reviewed literature supporting the efficacy and safety of this chemotherapy combination, over single-agent treatment, as maintenance therapy in NSCLC.

Neoadjuvant and Adjuvant Treatment for NSCLC

There are a number of randomized controlled trials investigating the role of pemetrexed in the neoadjuvant, adjuvant and chemoradiation settings. At this time, only Phase I and II studies have been published with mixed findings. A randomized phase II trial conducted to assess the efficacy and safety of pemetrexed with thoracic radiation concluded that, "We should await the results of ... large trials before incorporating pemetrexed or cetuximab in routine clinical practice for the treatment of patients with locally advanced NSCLC". In 2016, results were published from the PROCLAIM trial, a Phase III randomized trial evaluating the efficacy of pemetrexed-cisplatin doublet as a component of chemoradiation therapy for locally advanced non-squamous NSCLC compared to the standard of care, etoposide-cisplatin doublet in this setting. The trial randomly enrolled 599 individuals 1:1 into the two study arms with a primary objective of identifying superiority in OS. The trial was halted early due to futility (HR, 0.98; 95% CI, 0.79-1.20; $p=0.831$). Superiority of pemetrexed-cisplatin doublet, over standard of care etoposide-cisplatin with thoracic radiation therapy, was not demonstrated in unresectable NSCLC. The pemetrexed arm did however consistently demonstrate fewer grade 3 and 4 neutropenic and thrombocytopenic events. Further research is needed to more definitely determine the efficacy and safety of pemetrexed in neoadjuvant, adjuvant and chemoradiation settings over current standard of care chemotherapy regimens.

Ovarian Cancer

The current NCCN CPG in Oncology for ovarian cancer includes a recommendation for the use of pemetrexed for the second-line treatment of platinum-resistant, recurrent or progressive ovarian cancer (NCCN, [2018](#)). The 2A recommendation is based on a phase II trial conducted by Miller and colleagues designed to estimate antitumor activity of pemetrexed in women with persistent or recurrent platinum-resistant epithelial ovarian or primary peritoneal cancer. A total of 51 women were enrolled in the study and treatment was continued until disease progression or intolerable toxicities. The study also sought to identify the extent of toxicities. The study successfully identified antitumor activity and median PFS was 2.9 months with an OS of 11.4 months.

Vergote and colleagues conducted a randomized Phase II trial in 102 women with platinum-resistant disease. Study participants were treated with standard versus high-dose pemetrexed; the ORR was 9.3% and 10.4%, respectively. Similar to Miller and colleagues, PFS was 2.8 months in both arms with the standard-dose arm experiencing more favorable toxicities. A small number of additional phase II trials have appeared in the literature assessing safety and efficacy of pemetrexed combination chemotherapies in the treatment of recurrent or persistent ovarian cancer.

Bladder Cancer

The NCCN CPGs in Oncology for bladder cancer include a recommendation for the use of pemetrexed as a second-line treatment for metastatic bladder cancer (NCCN, [2018](#)). The 2A

recommendation is based on two phase II studies. In 2006, Sweeney and colleagues enrolled 47 participants with a performance status of one or better, satisfactory organ function, and previous treatment with one prior chemotherapy regimen for advanced transitional cell carcinoma (TCC) of the urothelium or relapsed within 1 year of treatment. The median TTP of disease was 2.9

Thymomas and Thymic Carcinomas

The NCCN CPGs in Oncology for thymomas and thymic carcinomas include a recommendation for the use of pemetrexed as a second-line treatment of thymomas and thymic carcinomas (NCCN, 2018). This is a rare neoplasm with an incidence in the United States of approximately 0.15 per 100,000 person-years; approximately 30% of new diagnoses are locally advanced or metastatic and inoperable. The 2A recommendation is based on two studies. The first, a phase II clinical trial conducted by Loehrer and colleagues evaluated the clinical activity of pemetrexed in individuals with thymomas and thymic carcinoma who had been previously treated. A total of 27 participants were enrolled with treatments scheduled every 3 weeks for a total of 6 cycles, or until disease progression or intolerable toxicities. A total of 2 participants had a CR and 2 others had PRs. Median time to progression for all participants was 45 weeks (thymomas = 45.5 weeks and thymic carcinomas = 45.1 weeks). This trial data was presented at a 2006 ASCO meeting but was not subsequently published in the peer-reviewed literature. In 2015, a small retrospective study was conducted by Liang and colleagues and evaluated 16 individuals diagnosed with thymic malignancies (n=10 with thymic carcinoma and n=6 with thymoma). All study enrollees had previously treated, unresectable, histologically confirmed invasive, recurrent or metastatic disease and received pemetrexed either as monotherapy (n=14) or combination therapy (n=2). Among the 6 individuals with thymoma, best response was 1 (17%) with a PR and 5 (83%) had SD. At a median follow-up of 21.2 months, the median PFS for those with thymomas was 13.8 months (95% CI, 4.9-22.6 months) and the median OS was 20.1 months (95% CI, 16.4-23.9 months). Among the 10 individuals with thymic carcinoma, best response was 1 (10%) PR, 5 (50%) SD, and 4 (40%) had progressive disease. At a median follow-up of 13.5 months, the median PFS in those with thymic carcinoma was 6.5 months (95% CI, 0.2-12.8 months) and the median OS was 12.7 months (95% CI, 2.9-22.5 months). Pemetrexed has demonstrated modest activity in this rare, difficult to treat malignancy.

Primary Central Nervous System (CNS) Lymphoma

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 (PCNSL; NCCN, 2017). The 2A recommendation is based on a single study conducted by Raizer and colleagues 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.

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, thymoma, thymic carcinoma, primary central nervous system lymphoma

Approved by Governing Bodies:

On February 4, 2004, FDA approved pemetrexed disodium for the treatment of patients with malignant pleural mesothelioma whose disease is either unresectable or who are otherwise not candidates for curative surgery. Also in 2004, the FDA approved pemetrexed for use as a single agent after previous chemotherapy for locally advanced or metastatic NSCLS.

On September 26, 2008, the U. S. Food and Drug Administration (FDA) approved pemetrexed injection (Alimta Injection, Eli Lilly and Company) for use in combination with cisplatin therapy for the initial treatment of patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC). Pemetrexed is not indicated for treatment of patients with squamous cell lung carcinoma.

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:

J9305 Injection, pemetrexed, 10 mg

References:

1. Alimta prescribing information. Eli Lilly and Company. 02/2015.
www.dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f5a860f3-37ec-429c-ae04-9c88d7c55c08.
2. American Cancer Society (ACS). Available at: <http://www.cancer.org/>.
3. Barlesi F, Scherpereel A, Gorbunova V, et al. Maintenance bevacizumab-pemetrexed after first-line cisplatin-pemetrexed-bevacizumab for advanced nonsquamous nonsmall-cell lung cancer: updated survival analysis of the AVAPERL (MO22089) randomized phase III trial. *Ann Oncol*. 2014; 25(5):1044-1052.
4. Barlesi F, Scherpereel A, Rittmeyer A, et al. Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab,

- cisplatin, and pemetrexed in advanced nonsquamous non-small-cell lung cancer: AVAPERL (MO22089). *J Clin Oncol*. 2013; 31(24):3004-301
5. Branden E, Hillerdal G, Kolbeck K, Koyi H. Pemetrexed and gemcitabine versus carboplatin and gemcitabine in non-small cell lung cancer: a randomized noninferiority phase II study in one center. *Oncologist*. 2015; 20(4):365.
 6. Burdett S, Pignon JP, Tierney J, et al. Adjuvant chemotherapy for resected early-stage non-small cell lung cancer. *Cochrane Database Syst Rev*. 2015;(3):CD011430.
 7. Carteni G, Manegold C, Garcia GM, et al. Malignant peritoneal mesothelioma-Results from the International Expanded Access Program using pemetrexed alone or in combination with a platinum agent. *Lung Cancer*. 2009; 64(2):211-218.
 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):1432-1440.
 9. Cohen MH, Cortazar P, Justice R, Approval Summary: pemetrexed maintenance therapy of advanced/metastatic nonsquamous, non-small cell lung cancer (NSCLC). *Oncologist*. 2010;15(12):1352-1358.
 10. Cohen MH, Johnson JR, Wang YC, et al. FDA drug approval summary: pemetrexed for injection (Alimta) for the treatment of non-small cell lung cancer. *Oncologist*. 2005; 10(6):363-368.
 11. Cohen MH, Justice R, Pazdur R. Approval summary: pemetrexed in the initial treatment of advanced/metastatic non-small cell lung cancer. *Oncologist*. 2009; 14(9):930-935.
 12. Galsky MD, Mironov S, Iasonos A, et al. Phase II trial of pemetrexed as second-line therapy in patients with metastatic urothelial carcinoma. *Invest New Drugs*. 2007; 25(3):265-270.
 13. Govindan R, Bogart J, Stinchcombe T, et al. Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407. *J Clin Oncol*. 2011; 29(23):3120-3125.
 14. Hagemann AR, Novetsky AP, Zigelboim I, et al. Phase II study of bevacizumab and pemetrexed for recurrent or persistent epithelial ovarian, fallopian tube or primary peritoneal cancer. *Gynecol Oncol*. 2013; 131(3):535-540.
 15. 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):1589-1597.
 16. Hazarika M, White RM, Johnson JR, Pazdur R. FDA drug approval summaries: pemetrexed (Alimta). *Oncologist*. 2004; 9(5):482-488.
 17. Hu X, Pu K, Feng X, et al. Role of gemcitabine and pemetrexed as maintenance therapy in advanced NSCLC: a systematic review and meta-analysis of randomized controlled trials. *PLoS One*. 2016; 11(3):e0149247.
 18. Jänne PA, Wozniak AJ, Belani CP, et al. Open-label study of pemetrexed alone or in combination with cisplatin for the treatment of patients with peritoneal mesothelioma: outcomes of an expanded access program. *Clin Lung Cancer*. 2005; 7(1):40-46.
 19. Karayama M, Inui N, Fujisawa T, et al. Maintenance therapy with pemetrexed and bevacizumab versus pemetrexed monotherapy after induction therapy with carboplatin, pemetrexed, and bevacizumab in patients with advanced non-squamous non-small cell lung cancer. *Eur J Cancer*. 2016; 58:30-37.

20. Kulkarni S, Vella ET, Coakley N, et al. The use of systemic treatment in the maintenance of patients with non-small cell lung cancer: a systematic review. *J Thorac Oncol.* 2016; 11(7):989-1002.
21. 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.
22. Li X, Wang H, Lin W, Xu Q. Efficacy of combining targeted therapy with pemetrexed or docetaxel as second-line treatment in patients with advanced non-small-cell lung cancer: a meta-analysis of 14 randomized controlled trials. *Curr Med Res Opin.* 2014; 30(11):2295-2304.
23. Liang Y, Padda SK, Riess JW, et al. Pemetrexed in patients with thymic malignancies previously treated with chemotherapy. *Lung Cancer.* 2015; 87(1):34-38.
24. Loehrer P, Yiannoutsos C, Dropcho S, et al. A phase II trial of pemetrexed in patients with recurrent thymoma or thymic carcinoma. *J of Clin Onco*, 2006 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 24, No 18S (June 20 Supplement), 2006:7079.
25. Masters GA, Temin S, Azzoli CG, et al. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol.* 2015; 33(30):3488-3515.
26. Matulonis UA, Horowitz NS, Campos SM, et al. Phase II study of carboplatin and pemetrexed for the treatment of platinum-sensitive recurrent ovarian cancer. *J Clin Oncol.* 2008; 26(35):5761-5766.
27. 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):2686-2691.
28. National Cancer Institute (NCI). Pemetrexed Disodium. Last updated on October 25, 2011. Available at: www.cancer.gov/cancertopics/druginfo/pemetrexedisodium.
29. National Cancer Institute (NCI). Bladder Cancer Treatment (PDQ). Revised February 18, 2016. Available at: www.cancer.gov/.
30. National Cancer Institute (NCI). Malignant Mesothelioma Treatment (PDQ). Revised October 14, 2016. Available at: www.cancer.gov/.
31. National Cancer Institute (NCI). Non-small Cell Cancer Treatment (PDQ). Revised July 07, 2016. Available at: www.cancer.gov/.
32. National Cancer Institute (NCI). Ovarian Epithelial, Fallopian Tube, and Primary Peritoneal Cancer Treatment (PDQ). Revised August 12, 2016.
33. National Cancer Institute (NCI). Primary CNS Lymphoma Treatment (PDQ). Revised August 12, 2016.
34. National Cancer Institute (NCI). Thymomas and Thymic Carcinomas Treatment (PDQ). Revised February 04, 2015.
35. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Version 3.2018. www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
36. NCCN Clinical Practice Guidelines in Oncology. Malignant Pleural Mesothelioma. Version 2.2018. www.nccn.org/professionals/physician_gls/pdf/mpm.pdf.
37. NCCN Drugs & Biologics Compendium. Pemetrexed. www.nccn.org/professionals/drug_compendium/MatrixGenerator/Matrix.aspx?AID=44.

38. NCCN Clinical Practice Guidelines in Oncology. Central Nervous System Cancers. Version 1.2017. www.nccn.org/professionals/physician_gls/pdf/cns.pdf.
39. NCCN Clinical Practice Guidelines in Oncology. Bladder Cancer. Version 2.2018. www.nccn.org/professionals/physician_gls/pdf/bladder.pdf.
40. NCCN Clinical Practice Guidelines in Oncology. Ovarian Cancer. Version 1.2018. www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf.
41. NCCN Clinical Practice Guidelines in Oncology. Thymomas and Thymic Carcinomas. Version 2.2018. www.nccn.org/professionals/physician_gls/pdf/thymic.pdf.
42. Patel JD, Hensing TA, Rademaker A, et al. Phase II study of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2009; 27(20):3284-3289.
43. Patel JD, Socinski MA, Garon EB, et al. PointBreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2013; 31(34):4349-4357.
44. Paz-Ares LG, de Marinis F, Dediu M, et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2013; 31(23):2895-2902.
45. Paz-Ares L, Mezger J, Ciuleanu TE, et al. Necitumumab plus pemetrexed and cisplatin as first-line therapy in patients with stage IV non-squamous non-small-cell lung cancer (INSPIRE): an open-label, randomised, controlled phase 3 study. *Lancet Oncol*. 2015; 16(3):328-337.
46. Pemetrexed Disodium (Alimta). In: DrugPoints® System (electronic version). Truven Health Analytics, Greenwood Village, CO. Updated August 30, 2017. Available at: www.micromedexsolutions.com.
47. Peterson P, Park K, Fossella F, et al. Is Pemetrexed more effective in adenocarcinoma and large cell lung cancer than in squamous cell carcinoma? A retrospective analysis of a phase III trial of pemetrexed vs docetaxel in previously treated patients with advanced non-small cell lung cancer (NSCLC). *J Thorac Oncol*. 2012 World Conference on Lung Cancer. 2007; 2(8):S8510.
48. Pilkington G, Boland A, Brown T, et al. A systematic review of the clinical effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer. *Thorax*. 2015; 70(4):359-367.
49. Pujol JL, Paz-Ares L, de Marinis F, et al. Long-term and low-grade safety results of a phase III study (PARAMOUNT): maintenance pemetrexed plus best supportive care versus placebo plus best supportive care immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. *Clin Lung Cancer*. 2014; 15(6):418-425.
50. Raizer JJ, Rademaker A, Evens AM, et al. Pemetrexed in the treatment of relapsed/refractory primary central nervous system lymphoma. *Cancer*. 2012; 118(15):3743-3748.
51. Rittmeyer A, Gorbunova V, Vikström A, et al. Health-related quality of life in patients with advanced nonsquamous non-small-cell lung cancer receiving bevacizumab or bevacizumab-plus-pemetrexed maintenance therapy in AVAPERL (MO22089). *J Thorac Oncol*. 2013; 8(11):1409-1416.

52. Santoro A, O'Brien ME, Stahel RA, et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemo-naïve patients with malignant pleural mesothelioma: results of the International Expanded Access Program. *J Thorac Oncol.* 2008 3(7):756-763.
53. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol.* 2008; 26(21):3543-3551.
54. Sehouli J, Alvarez AM, Manouchehrpour S, et al. A phase II trial of pemetrexed in combination with carboplatin in patients with recurrent ovarian or primary peritoneal cancer. *Gynecol Oncol.* 2012; 124(2):205-209.
55. Senan S, Brade A, Wang LH, et al. PROCLAIM: Randomized phase III trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. *J Clin Oncol.* 2016; 34(9):953-962.
56. Shi SB, Wang M, Tian J, et al. MicroRNA 25, microRNA 145, and microRNA 210 as biomarkers for predicting the efficacy of maintenance treatment with pemetrexed in lung adenocarcinoma patients who are negative for epidermal growth factor receptor mutations or anaplastic lymphoma kinase translocations. *Transl Res.* 2016; 170:1-7.
57. Sio T, Ko J, Gudena V, et al. Chemotherapeutic and targeted biologic agents for metastatic bladder cancer: a comprehensive review. *Int J Urol.* 2014; 21(7):630-637.
58. Sun CT, Xu X, Sheng W, et al. A meta-analysis of pemetrexed-based doublet compared with pemetrexed alone for the second-line treatment of advanced non-small-cell lung cancer. *Bratisl Lek Listy.* 2014; 115(4):233-237.
59. Sweeney CJ, Roth BJ, Kabbinnavar FF, et al. Phase II study of pemetrexed for second-line treatment of transitional cell cancer of the urothelium. *J Clin Oncol.* 2006; 24(21):3451-3457.
60. Tong S, Fan K, Jiang K, et al. Increased risk of severe infections in non-small-cell lung cancer patients treated with pemetrexed: a meta-analysis of randomized controlled trials. *Curr Med Res Opin.* 2016 Sep 22:1-7. [Epub ahead of print].
61. UpToDate. Overview of the treatment of advanced non-small cell lung cancer.
62. UpToDate. Epidemiology of malignant pleural mesothelioma.
63. Vergote I, Calvert H, Kania M, et al. A randomised, double-blind, phase II study of two doses of pemetrexed in the treatment of platinum-resistant, epithelial ovarian or primary peritoneal cancer. *Eur J Cancer.* 2009; 45(8):1415-1423.
64. 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.
65. Xiao HQ, Tian RH, Zhang ZH, et al. Efficacy of pemetrexed plus platinum doublet chemotherapy as first-line treatment for advanced nonsquamous non-small-cell-lung cancer: a systematic review and meta-analysis. *Onco Targets Ther.* 2016; 9:1471-1476.
66. Zalcman G, Mazieres J, Margery J, et al.; French Cooperative Thoracic Intergroup (IFCT). Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet.* 2016; 387(10026):1405-1414.

Policy History:

New policy created, effective date March 1, 2016

Medical Policy Group, January 2017 (2): Updates to Key Points, Key Words, and Approved by Governing Bodies, and References; Policy section updated to include criteria for thymic cancers and thymomas, and added criteria for NSCLC when used as subsequent therapy in combination with cisplatin or carboplatin for sensitizing EGFR or ALK positive tumors.

Medical Policy Group, March 2018 (2): Updates to Key Points and References; Policy section updated to include criteria for NSCLC with ROS1 and BRAF V600E positive tumors, updated malignant mesothelioma criteria, and added criteria for lab value assessment during treatment per FDA recommendations.

Available for comment March 1, 2018 through April 15, 2018.

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.