



CIGNA HEALTHCARE COVERAGE POSITION

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Coverage Position Number 5104

Subject **Pemetrexed (Alimta®)**

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Related Coverage Positions

INSTRUCTIONS FOR USE

Coverage Positions are intended to supplement certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Positions are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Position. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Positions. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Positions and; 4) the specific facts of the particular situation. Coverage Positions relate exclusively to the administration of health benefit plans. Coverage Positions are not recommendations for treatment and should never be used as treatment guidelines. ©2005 CIGNA Health Corporation

Coverage Position

CIGNA HealthCare covers pemetrexed (Alimta®) as medically necessary when ANY of the following indications are met:

- in combination with cisplatin for the treatment of malignant pleural mesothelioma in patients who are not candidates for surgery
- as second-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy

CIGNA HealthCare does not cover pemetrexed (Alimta®) for the following indications because it is considered experimental, investigational or unproven:

- first-line treatment of NSCLC
- treatment of breast cancer
- treatment of ovarian cancer
- treatment of previously treated colorectal cancer
- treatment of bladder cancer
- treatment of gastric cancer

General Background

Pemetrexed, an antifolate antineoplastic agent, was approved by the U.S. Food and Drug Administration (FDA) in February 2004. It is labeled as a single agent for the treatment of patients with advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. Pemetrexed is also labeled for

use with cisplatin for the treatment of malignant pleural mesothelioma (MPM) in patients whose disease is unresectable or if the patients are not candidates for surgery.

Pemetrexed is an antineoplastic folate antagonist. It inhibits thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase. These enzymes are all folate-dependent and involved in the de novo biosynthesis of thymidine and purine nucleotides. The end result is a disruption of cellular replication.

Pemetrexed has a steady state volume of distribution of 16.1 L and is 81% bound to plasma proteins. Pemetrexed is not metabolized to an appreciable extent. It is eliminated in the urine with 70-90% of the dose recovered unchanged within 24 hours of administration. The elimination half-life is 3.5 hours in patients with normal renal function (a creatinine clearance \geq 90 mL/min). Total systemic clearance is 91.8 mL/min. The pharmacokinetics of pemetrexed does not change over multiple treatment cycles.

Pemetrexed has been evaluated as an antifolate antineoplastic agent in phase I and II clinical trials since the late 1990s. It has been studied as a single agent and in combination chemotherapy for a variety of cancers including MPM, non-small-cell lung cancer, breast cancer, colorectal carcinoma, bladder cancer, and cervical carcinoma.

Malignant Pleural Mesothelioma (MPM)

Pemetrexed has been evaluated for the treatment of MPM in three clinical trials and several abstracts. In all three clinical trials, patients were not candidates for surgical resection and had not received prior chemotherapy. Pemetrexed was either studied as a single agent or in combination with cisplatin or carboplatin. No patient in these trials had a complete response, but partial response rates ranged from 14-41%. Myelosuppression was the primary dose limiting toxicity, but in general treatment was well-tolerated and patients were able to complete a median of six courses in each study. A phase III clinical trial is currently underway to compare pemetrexed to best supportive care in previously treated patients.

Vogelzang et al. (2003) designed a single-blind, placebo controlled, experimental trial to determine if combination therapy of pemetrexed and cisplatin demonstrated better survival duration than cisplatin alone in 448 patients with MPM. The primary outcome was survival. Secondary outcomes measured included time to progressive disease, time to treatment failure, tumor response rate, and duration of response. Patients received pemetrexed (500 mg/m²) and cisplatin (75 mg/m²) or received cisplatin (75 mg/m²) following a normal saline placebo infusion. The study protocol changed to require supplementation with folic acid and cyanocobalamin after three of the first 43 patients randomized to the pemetrexed/cisplatin arm died from treatment related toxicities, suggesting deficiency in folic acid and vitamin B₁₂ stores. Median survival time for patients who received both pemetrexed and cisplatin was 12.1 months versus 9.3 months for those who receive cisplatin alone (p=0.012). In the fully and partially supplemented groups, the median survival time of the pemetrexed/cisplatin group was 13.2 months versus 9.4 months for the cisplatin only group (p=0.022). There was no statistically significant difference between the never supplemented groups. Median time to disease progression was 5.7 months in the pemetrexed/cisplatin group and 3.9 months in the cisplatin only group (p=0.001). All responses were partial responses; 41.3% responded in the pemetrexed/cisplatin group and 16.7% responded in the cisplatin group (p \leq 0.001). The most common toxicities in the pemetrexed/cisplatin group were grade 3/4 neutropenia (27.9%) and leukopenia (17.7%). The incidence of neutropenia in the never/partial supplemented patients (41.4%) was significantly higher than in the fully supplemented patients (23.3%; p=0.011). The fully supplemented patients in the pemetrexed/cisplatin arm consistently experienced less toxicity. The authors concluded that the combination of pemetrexed and cisplatin significantly improved survival time for patients with MPM.

Scagliotti et al. (2003) designed a non-blinded experimental phase II study to determine the efficacy of pemetrexed alone in patients with advanced MPM. They studied 64 patients with histological diagnosed MPM, who were not eligible for surgery. These patients also had to have bidimensional and/or unidimensional measurable lesions by computed tomography (CT) or magnetic resonance imaging (MRI). The primary outcome was tumor response. Secondary outcomes included duration of response, survival, time to progressive disease, time to treatment failure, quality of life, and pulmonary function tests. The study design initially was to enroll 20 patients and if two patients achieved a response, 21 more patients were to be enrolled. Toward the end of the enrollment of the first 20 patients, the protocol was amended

to require that patients be supplemented with folic acid and cyanocobalamin and at least 41 more patients were to be enrolled. The starting dose of pemetrexed was 500 mg/m² day 1 with dexamethasone 4 mg given twice daily on day 0, day 1, and day 2. Forty-three patients were fully supplemented with folic acid and cyanocobalamin and 21 patients were not supplemented. Five of the 21 non-supplemented patients started receiving supplementation after the start of pemetrexed therapy. Fully supplemented patients completed more cycles of therapy compared to those who were not supplemented. No patient experienced a complete response; however, nine of the 64 patients (14.1%) had a partial response to the therapy. Of the nine patients who had a partial response, seven of them were in the fully supplemented group. The median survival time for all patients was 10.7 months. Supplemented patients had a median survival time of 13.0 months versus 8.0 months for non-supplemented patients. The median duration of response among the partial responding patients was 8.5 months. Fatigue and febrile neutropenia were the most common adverse events reported in both groups followed by nausea, vomiting, and stomatitis. Incidence of grade 3 or 4 neutropenia was 52.4% in non-supplemented patients and 9.3% in supplemented patients. Seven patients withdrew from the study due to an adverse event. Five of these seven patients were in the non-supplemented group. The authors concluded that pemetrexed has a modest response rate of 14.1% as a single agent in MPM and that folic acid and cyanocobalamin supplemented patients have better toleration for therapy.

Hughes et al. (2002) conducted a phase I trial to evaluate the clinical efficacy and pharmacokinetic properties of pemetrexed in combination with carboplatin for the treatment of MPM. Twenty-seven patients were enrolled in a dose escalation study. Seventeen patients (63%) had stage IV disease and eight patients (30%) had stage III disease. Five dose levels were used. Pemetrexed dose ranged from 400 to 600 mg/m² and carboplatin dose was based on area under the curve (AUC) levels of 4-6 mg/mL x min. One patient was begun on the first dose level and observed for 21 days. If the patient tolerated this dose combination, additional patients were enrolled. No interpatient dose escalation was permitted in the study. If a dose limiting toxicity was observed in the first three patients of any dose level then an additional three patients were recruited. If the same dose limiting toxicity occurred in two of the six patients, dose escalation was stopped and that dose defined the maximum tolerated dose. The overall response rate was 32%. No patient had a complete response. Eight patients had a partial response and 14 patients had stable disease. Median progression-free survival was 305 days and median overall survival was 451 days. The major dose limiting toxicity was myelosuppression; 19 out of 27 patients experienced either grade 3 or 4 neutropenia. The median number of treatment courses was six (range 1-10), indicating the drugs were generally well tolerated. Overall, the authors state the recommended dose is pemetrexed 500 mg/m² and carboplatin AUC 5 mg/mL x min. At the time this study was conducted, it was not yet known that vitamin supplementation should be routinely administered.

Janne et al. (2004) recently presented data from a phase II clinical trial that evaluated the use of pemetrexed plus gemcitabine in patients with MPM. Forty-nine patients were treated with pemetrexed 500 mg/m², given on day 8, with vitamin supplementation and gemcitabine 1250 mg/m² given on days 1 and 8. The treatment cycle was repeated every 21 days. The overall response rate in this study was 20%.

In conclusion, pemetrexed offers benefit to patients with MPM who are not candidates for surgical resection and who have not received prior chemotherapy. Response rates with pemetrexed as a single agent are 14%, compared to other single-agent studies, which report response rates from 0-15%. When pemetrexed is used in combination with cisplatin, response rates go up to 41%. This is an improvement to previous studies, which have reported response rates of 20-30% with combination chemotherapy (using platinum, anthracyclines, gemcitabine, or antimetabolites).

Non-Small Cell Lung Cancer (NSCLC)

There are six published clinical trials evaluating the use of pemetrexed in NSCLC. There is one comparative trial and five descriptive, open-label phase II trials. The number of patients studied ranges from 31-81 patients in the observational studies and 571 patients in the comparative trial. All patients in these studies had at least stage III or IV disease. In four of the studies, patients were chemotherapy naïve. Pemetrexed was used as a single agent in four studies while the other two studies evaluated the combination of pemetrexed and cisplatin. Vitamin supplementation with folic acid and cyanocobalamin was employed in only one trial. Overall response rates for single agent pemetrexed range from 8.8-23%.

Response rates for the combination of pemetrexed and cisplatin range from 39-41%. In all studies, median time to disease progression ranged from 2-6 months. Dexamethasone was used to prevent cutaneous toxicity in five of the six trials. When pemetrexed was compared head-to-head with docetaxel, there were no differences in response rates but the pemetrexed group had significantly fewer adverse reactions (e.g., grade 3 or 4 neutropenia 5.3% vs. 40.2%).

There is only one comparative published trial with pemetrexed for NSCLC. Hanna et al. (2004) compared pemetrexed and docetaxel in 571 patients with advanced NSCLC previously treated with chemotherapy. Docetaxel is FDA-labeled as second line treatment for advanced NSCLC. Patients with grade III or IV disease who had been treated with only one prior chemotherapy regimen were randomized to either pemetrexed 500 mg/m² (n=283) or docetaxel 75 mg/m² (n= 288) given on day 1 and repeated every 21 days. Patients were included if they had a performance status of 0 to 2 and adequate bone marrow, renal and liver function. Patients who received pemetrexed also received folic acid, cyanocobalamin and dexamethasone. The primary objective was to compare overall survival between the two treatment groups. Secondary endpoints included progression-free survival, time to disease progression, time to treatment failure, duration of response and adverse reactions. There was no difference in overall survival between the groups, 29.7% for each group. Overall response rate (complete response + partial response) was 9.1% in the pemetrexed group and 8.8% in the docetaxel arm. There was also no difference between the groups with regard to progression-free survival, time to disease progression, and time to treatment failure. There was also no difference between the groups in quality of life, as assessed by the Lung Cancer Symptom Scale (p=0.144). The only significant differences found in this study were related to adverse reactions. The percent of patients experiencing Grade 3 or 4 hematologic toxicity was 5.3% in the pemetrexed treated patients and 40.2% in the docetaxel treated patients (p<0.001). For patients with febrile neutropenia, the rates were 1.9% and 12.7%, respectively (p<0.001). For the docetaxel group, 13.4% of patients had greater than one hospitalization compared to 1.5% of pemetrexed-treated patients, (p<0.001). The use of colony stimulating factors was higher in the docetaxel group, 19.2% versus 2.6%, (p<0.001). Overall, pemetrexed and docetaxel are equally efficacious for the treatment of advanced lung cancer but pemetrexed has less toxicity.

The most common adverse drug reactions reported with pemetrexed include fatigue, dyspnea, anorexia, neutropenia, leukopenia, anemia, nausea, chest pain, neuropathy, fever, infection, stomatitis, edema, and rash. Patients must be premedicated with a corticosteroid, folic acid and cyanocobalamin to reduce the risk of gastrointestinal, hematological and dermatological adverse reactions.

Pemetrexed is eliminated via glomerular filtration and tubular secretion. Concomitant administration of nephrotoxic agents or those that undergo renal tubular secretion could result in the delayed clearance of pemetrexed. In patients with mild-to-moderate renal insufficiency, non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided two to five days before, the day of, and two days after receiving a dose of pemetrexed to minimize the potential interaction of increased toxicity of pemetrexed with NSAIDs.

The recommended dose of pemetrexed is 500 mg/m² administered intravenously over 10 minutes on day 1 of a 21 day cycle. It may be given as a single agent for NSCLC or in combination with cisplatin for MPM. The recommended cisplatin dose is 75 mg/m², infused 30 minutes after the end of the pemetrexed infusion over two hours. Dosing adjustments are recommended for patients who experience any of the following: hematologic toxicity, nonhematologic Grade 3 or 4 toxicity, diarrhea requiring hospitalization, or Grade 3 or 4 neurotoxicity.

Overall, for NSCLC, pemetrexed is equivalent to docetaxel and for MPM the combination of pemetrexed and cisplatin is better than cisplatin alone. The role of pemetrexed may be to provide symptom relief and improve survival while minimizing the adverse effects associated with chemotherapy.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

| CPT®* Codes | Description |
|-------------|-------------|
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| HCPCS Codes | Description |
|-------------|-------------|
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| ICD-9-CM Diagnosis Codes | Description |
|--------------------------|-------------|
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Experimental/Investigational/Unproven/Not Covered:

| CPT* Codes | Description |
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| HCPCS Codes | Description |
|-------------|-------------|
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| ICD-9-CM Diagnosis Codes | Description |
|--------------------------|-------------|
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*Current Procedural Terminology (CPT®) ©2004 American Medical Association: Chicago, IL.

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