Clinical Policy Bulletin: 
Pralatrexate (Folotyn)

Number: 0740

Policy

Aetna considers pralatrexate (Folotyn) medically necessary for persons with the following conditions:

- Adult T-cell lymphoma
- Anaplastic large cell lymphoma
- Angioimmunoblastic T-cell lymphoma
- Enteropathy-associated T-cell lymphoma
- Mycosis fungoides or Sezary syndrome
- Peripheral T-cell lymphoma not otherwise specified
- Primary cutaneous anaplastic large cell lymphoma

Aetna considers pralatrexate experimental and investigational for the following criteria:

- Use not approved by the FDA; AND
- The use is unapproved and not supported by the literature or evidence as an accepted off-label use

Note: Vitamin B-12 supplementation is considered medically necessary for members taking pralatrexate (see CPB 0536 - Vitamin B-12 Therapy).

Background

Pralatrexate, a 10-deazaaminopterin derivative, is a novel anti-folate designed to have high affinity for the reduced folate carrier type 1; inhibiting dihydrofolate reductase. Pre-clinical and clinical studies have demonstrated that pralatrexate has significant activity against peripheral T-cell lymphoma (PTCL), an often aggressive type of non-Hodgkin's lymphoma (NHL). The dose-limiting toxicity (DLT) for pralatrexate is mucositis, which
could be abrogated with folic acid and vitamin B-12 supplementation. Because of the relative rarity of this group of diseases, large-scale prospective clinical trials are difficult to implement (Rosenstein and Link, 2008; Rueda et al, 2009).

Molina (2008) stated that pralatrexate was developed to overcome the limitations of the folate analog, methotrexate. Compared with methotrexate in pre-clinical studies, pralatrexate demonstrated superior intra-cellular transport via the reduced folate carrier, and increased accumulation within cells by enhanced polyglutamylation. Pre-clinical studies in-vitro and in models of B-cell lymphomas, T-cell lymphomas and non-small cell lung carcinoma (NSCLC) indicated that pralatrexate exhibited anti-tumor activity that was superior to the activity of other anti-folates. The administration of pralatrexate to patients with T-cell lymphomas and NSCLC resulted in significant tumor remissions. At the time of publication, pralatrexate was in phase II clinical trials for the treatment of PTCL, a phase I/II trial in combination with gemcitabine for the treatment of NHL, and a phase Ib trial in comparison with erlotinib in patients with NSCLC. Because of the limited therapies available for PTCL, pralatrexate could have a secure niche for the treatment of this indication, if ongoing clinical trials and future phase III trials confirm the efficacy of the drug. The authors noted that, in contrast, for pralatrexate to be incorporated into the accepted treatment options for NSCLC, the drug will need to prove clear superiority to established agents.

In a phase II study, Krug et al (2007) examined the response rate of malignant pleural mesothelioma to pralatrexate at an intravenous dose of 135 mg/m2 every 2 weeks. After a protocol amendment, patients were supplemented with vitamin B-12 and folic acid at the time of starting therapy. A total of 16 patients were enrolled. No complete or partial responses were observed. Two patients with epithelioid histology had minor responses; 3 other patients remained on study with stable disease for 9, 9, and 48 months. The median time to progression was 3 months. The overall median survival time was 7 months (95 % confidence interval [CI]: 3.2 to 16.2 months) and the 1-year survival was 31 % (95 % CI: 15 % to 65 %). Three patients (19 %) had grade 2 stomatitis, 8 (50 %) had grade 3, and 1 (6 %) had grade 4. The authors concluded that with this particular dose and schedule, pralatrexate as a single agent had no activity in malignant pleural mesothelioma.

In phase I study, Azzoli et al (2007) determined the maximum tolerated dose (MTD) and toxicity of pralatrexate plus paclitaxel or docetaxel in patients with advanced cancer. Pralatrexate was administered intravenously every 2 weeks (days 1 and 15) in a 4-week cycle. Depending on the taxane used and dose being tested, the taxane was administered on days 1 and 15; days 2 and 16; or days 1, 8, and 15. In the latter part of the study, patients in the docetaxel arm were treated with vitamin B-12 and folic acid supplementation to mitigate toxicity and allow pralatrexate dose escalation. For the combination of pralatrexate plus paclitaxel without vitamin supplementation, dose-limiting stomatitis and peripheral neuropathy were encountered at the lowest dose levels tested. For pralatrexate plus docetaxel plus vitamin supplementation, pralatrexate 120 mg/m2(2) plus docetaxel 35 mg/m(2) administered on the same day every other week was defined as the MTD and schedule, with DLT at higher dose combinations including stomatitis and asthenia. Significant anti-tumor activity was observed for this combination in patients with NSCLC. The authors concluded that pralatrexate (120 mg/m2(2)) plus docetaxel (35 mg/m (2)) plus vitamin supplementation is well-tolerated with signs of efficacy against NSCLC that merit phase II testing.
O'Connor et al (2009) determined the MTD and efficacy of pralatrexate in patients with lymphoma. Pralatrexate, initially given at a dose of 135 mg/m(2) on an every-other-week basis, was associated with stomatitis. A re-designed, weekly phase I/II study established an MTD of 30 mg/m(2) weekly for 6 weeks every 7 weeks. Patients were required to have relapsed/refractory disease, an absolute neutrophil greater than 1,000/microL, and a platelet count greater than 50,000/microL for the first dose of any cycle. The every-other-week, phase II experience was associated with an increased risk of stomatitis and hematologic toxicity. On a weekly schedule, the MTD was 30 mg/m(2) weekly for 6 weeks every 7 weeks. This schedule modification resulted in a 50 % reduction in the major hematologic toxicities and abrogation of the grades 3 to 4 stomatitis. Stomatitis was associated with elevated homocysteine and methylmalonic acid, which were reduced by folate and vitamin B-12 supplementation. Of 48 assessable patients, the overall response rate was 31 % (26 % by intention-to-treat), including 17 % who experienced complete remission (CR). When analyzed by lineage, the overall response rates were 10 % and 54 % in patients with B-cell and T-cell lymphomas, respectively. All 8 patients who experienced CR had T-cell lymphoma, and 4 of the 6 patients with a partial remission were positron emission tomography negative. The duration of responses ranged from 3 to 26 months. The authors concluded that pralatrexate has significant single-agent activity in patients with relapsed/refractory T-cell lymphoma.

In September 2009, the Food and Drug Administration (FDA) approved pralatrexate (Folotyn), designated as an orphan drug, for the treatment of PTCL, which is a relatively rare disease occurring in less than 9,500 patients each year in the United States. Folotyn was approved under the FDA's accelerated approval process. It is indicated for patients who have relapsed, or have not responded well to other forms of chemotherapy. The FDA approved Folotyn based on evidence that it reduces tumor size, because tumor shrinkage is considered reasonably likely to predict a clinical benefit such as extending the survival of cancer patients. Tumor shrinkage was seen on imaging scans in 1 study. Of 109 patients with PTCL in the trial, 27 % had reduction in tumor size. The most common adverse reactions associated with the use of Folotyn were irritation or sores of the mucous membranes such as the lips, the mouth, and the digestive tract, low platelet cell counts, low white blood cell counts, fever, nausea, and fatigue. Patients treated with Folotyn should take folate and vitamin B-12 supplements to reduce mucous membrane irritation.

Marchi and colleagues (2010) examined the in-vitro and in-vivo activities of pralatrexate alone and in combination with bortezomib in PTCL. In-vitro, pralatrexate and bortezomib exhibited concentration- and time-dependent cytotoxicity against a broad panel of T-lymphoma cell lines. Pralatrexate showed synergism when combined with bortezomib in all cell lines studied. Pralatrexate also induced potent apoptosis and caspase activation when combined with bortezomib across the panel. Cytotoxicity studies on normal peripheral blood mononuclear cells showed that the combination was not more toxic than the single agents. In a severe combined immunodeficient-beige mouse model of transformed cutaneous T-cell lymphoma, the addition of pralatrexate to bortezomib enhanced efficacy compared with either drug alone. The authors concluded that collectively, these data suggest that pralatrexate in combination with bortezomib represents a novel and potentially important platform for the treatment of PTCL.

Zain and O’connor (2010) described how pralatrexate is being combined with other agents in the pre-clinical and clinical arenas. The authors stated that pralatrexate is a unique anti-folate that has been rationally designed to have a high affinity for the reduced
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folate receptor and the enzyme folicpolyglutamy synthetase. It is active in PTCL and NSCLC. It is now being studied in combination with other chemotherapeutic and targeted agents for the treatment of hematological malignancies.

In a phase II b clinical trial, Kelly and colleagues (2012) evaluated pralatrexate activity in NSCLC by estimating overall survival (OS) relative to erlotinib in patients with relapsed/refractory disease. In 43 centers across 6 countries, patients were randomized 1:1 to receive intravenous pralatrexate 190 mg/m on days 1 and 15 of a 28-day cycle, or oral erlotinib 150 mg/day. The primary objective was to estimate OS in all patients and pre-specified subgroups using relative comparisons of hazard ratios (HRs). Secondary endpoints included progression-free survival, response rate, and safety. Key eligibility criteria included: (i) greater than or equal to 1 prior platinum-based therapy, (ii) Eastern Cooperative Oncology Group performance status of 0 to 1, and (iii) a smoking history of 100 cigarettes or more. A total of 201 patients were randomized. A trend toward improvement in OS favoring pralatrexate was observed with an HR of 0.84 (95 % CI: 0.61 to 1.14) in the intent-to-treat population. This favorable survival result was seen in most prespecified subgroups for pralatrexate. The largest reduction in the risk of death was observed in patients with non-squamous cell carcinoma (n = 107; HR = 0.65; 95 % CI: 0.42 to 1.0). The most common grade 3 to 4 adverse event in the pralatrexate arm was mucositis (23 %). Discontinuation of pralatrexate for any grade of mucositis was 21 %. The authors concluded that pralatrexate demonstrated a trend toward improved survival relative to erlotinib in patients with advanced NSCLC. They stated that future studies should include a mucositis management plan to improve tolerability and maximize treatment benefit.

Abramovits et al (2012) stated that T-cell lymphoma accounts for 10 to 15 % of all cases of NHL in the United States (approximately 5,000 to 6,000 cases a year). Peripheral T-cell lymphoma comprises a subgroup of rare and aggressive NHL that develops from T cells in different stages of maturity outside of the thymus. Cutaneous T-cell lymphoma (CTCL) is a subgroup that falls within the T-cell lymphoma population but is classified differently than other PTCLs. Most cases of CTCL are considered indolent and can often be treated with less aggressive therapies. Eight percent to 55 % of CTCL cases undergo transformation, and once this transformation occurs, the disease acts similarly to other PTCLs and its classification changes to that of a PTCL. Transformed CTCL requires aggressive systemic therapy. Pralatrexate (PDX) is the first FDA-approved drug for relapsed and refractory PTCL and has also gained compendia approval for treatment of CTCL. Pralatrexate is an anti-folate chemotherapeutic inhibitor of dihydrofolatereductase. It has a high affinity for the one carbon-reduced folate carrier, which leads to better cellular internalization of the drug and has a greater anti-tumor effect than methotrexate. Several clinical trials have been conducted to evaluate the use of this drug in PTCL and other malignancies such as NSCLC.

Hui and colleagues (2012) reviewed the pharmacology, pharmacokinetics, clinical trials, adverse effects, dosage, and economic considerations of PDX. Peripheral T-cell lymphoma comprises approximately 15 to 20 % of all aggressive lymphomas and 5 to 10 % of all NHL. Advanced PTCL is often refractory to traditional first-line chemotherapy regimens. Pralatrexate has a higher potency than methotrexate and edatrexate. The safety and effectiveness of PDX have been demonstrated in the PROPEL trial, a prospective phase II trial in patients with relapsed or refractory PTCL. Patients with prior stem cell transplantation receiving PDX also had similar response rates. Pralatrexate was investigated on the treatment of relapsed or refractory cutaneous T-cell lymphoma,
Pralatrexate (Folotyn) previously treated advanced NSCLC, and other solid malignancies. Pralatrexate has similar side effects to other DHFR inhibitors. The most common side effect of PDX is mucositis. The recommended dose of PDX is 30 mg/m² once-weekly for 6 weeks in a 7-week cycle until disease progresses or unacceptable toxicity for PTCL and may require dose reduction or discontinuation. Patients should be supplemented with oral folic acid and intramuscular vitamin B-12 injections. The authors concluded that PDX provides clinical benefit to patients with relapsed or refractory PTCL with durable complete and partial responses in patients who had not responded to multiple prior treatment regimens.

Koch et al (2013) noted that balancing the safety and effectiveness of drugs is important for successful cancer therapy, as adverse reactions can prohibit the use of effective treatments. Pralatrexate is a novel anti-folate with a higher affinity for tumor cells than methotrexate, FDA-approved for use in relapsed and refractory PTCL and transformed mycosis fungoides (T-MF). Patients with T-MF have a higher incidence of adverse events than patients with other lymphomas, necessitating a lower recommended dose of 15 mg/m² (versus 30 mg/m² for PTCL). Dose-limiting toxicity mucositis occurs in about 25% of patients with T-MF, but milder mucositis is observed in almost all patients with T-MF, frequently leading to therapy discontinuation despite clinical response. Leucovorin rescue is the standard of care for high-dose methotrexate therapy, but has not been studied or recommended for use with PDX. These investigators reported their clinical experience using leucovorin with PDX (30 mg/m²) with good clinical response and no DLTs. The authors concluded that prophylactic leucovorin deserves further investigation in prospective clinical trials to allow patients with cutaneous lymphomas to receive the full benefit of PDX therapy without intolerable toxicity.

The British Committee for Standards in Haematology’s guidelines on “The management of mature T-cell and NK-cell neoplasms (excluding cutaneous T-cell lymphoma)” (Dearden et al, 2013) noted that “There are insufficient data to recommend novel agents such as gemcitabine, bendamustine, pralatrexate, and romidepsin”.

In a phase II clinical trial, Ho and colleagues (2014) examined the effects of pralatrexate with folic acid and B12 supplementation in patients with recurrent and/or metastatic head and neck squamous cell cancer (R/M HNSCC). This was a single-arm, Simon optimal 2-stage study. Patients with R/M HNSCC previously treated with chemotherapy were eligible. The study was initiated with a dosing schedule of pralatrexate 190 mg/m² bi-weekly on a 4-week cycle with vitamin supplementation. Due to toxicity concerns, the dosing was modified to 30 mg/m² weekly for 3 weeks in a 4-week cycle with vitamin supplementation. Radiologic imaging was to be obtained about every 2 cycles. A total of 13 subjects were enrolled; 12 were treated; 7 of the 12 patients had previously received greater than or equal to 2 lines of chemotherapy. The most common grade 3 toxicity was mucositis (3 patients). Seven patients did not complete 2 cycles of therapy due to progression of disease (n = 4), toxicity (n = 1), death (n = 1), and withdrawal of consent (n = 1). Two deaths occurred: one due to disease progression and the other was an unwitnessed event that was possibly related to pralatrexate. No clinical activity was observed. The median OS was 3.1 months. The study was closed early due to lack of efficacy. The authors concluded that pralatrexate does not possess clinical activity against previously treated R/M HNSCC. Evaluation of pralatrexate in other clinical settings of HNSCC management with special considerations for drug toxicity may be warranted.
Furthermore, the National Comprehensive Cancer Network’s Drugs & Biologics Compendium (2014) does not list head and neck squamous cell cancer and natural killer (NK)-cell neoplasms as recommended indications of pralatrexate.

CPT Codes / HCPCS Codes / ICD-9 Codes

Other CPT codes related to the CPB:

96374
96375
96379

HCPCS codes covered if selection criteria are met:

J9307 Injection, pralatrexate, 1 mg

ICD-9 codes covered if selection criteria are met:

200.60 - 200.68 Anaplastic large cell lymphoma
202.10 - 202.18 Mycosis fungoides [adult T-cell lymphoma]
202.20 - 202.28 Sezary’s disease
202.70 - 202.78 Peripheral T cell lymphoma [adult]
202.80 - 202.88 Other lymphoma

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

147.0 - 147.9 Malignant neoplasm of nasopharynx
150.0 - 150.9 Malignant neoplasm of esophagus
151.0 - 151.9 Malignant neoplasm of stomach
153.0 - 153.9 Malignant neoplasm of colon
154.0 - 154.8 Malignant neoplasm of rectum, rectosigmoid junction, and anus
155.1 Malignant neoplasm of intrahepatic bile duct
156.0 - 156.9 Malignant neoplasm of gall bladder and extrahepatic bile duct
157.0 - 157.9 Malignant neoplasm of pancreas
160.2 - 160.9 Malignant neoplasm of accessory sinuses (paranasal)
162.0 - 162.9 Malignant neoplasm of trachea, bronchus, and lung [non-small-cell lung cancer (NSCLC)]
163.0 - 163.9 Malignant neoplasm of pleura
164.0  Malignant neoplasm of thymus
171.0 - 171.9  Malignant neoplasm of connective and other soft tissue
172.0 - 172.9  Malignant neoplasm of skin
174.0 - 175.9  Malignant neoplasm of breast, female, male
176.1  Kaposi's sarcoma, soft tissue
180.0 - 180.9  Malignant neoplasm of cervix uteri
182.0 - 182.8  Malignant neoplasm of body of uterus
183.2  Malignant neoplasm of fallopian tube
185  Malignant neoplasm of prostate
189.0 - 189.9  Malignant neoplasm of kidney and other and unspecified urinary organs
193  Malignant neoplasm of thyroid gland
230.0 - 234.9  Carcinoma in situ

The above policy is based on the following references:


