09-J1000-18

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Reviewed: 02/12/14

Revised: 10/01/24

Subject: Pralatrexate (Folotyn™) IV

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DESCRIPTION:

Pralatrexate (Folotyn) is a novel antifolate that is structurally similar to methotrexate. It has been investigated as a treatment option for relapsed or refractory peripheral T-cell lymphoma (PTCL) and as a second-line option in the treatment of cutaneous T-cell lymphomas (CTCL), specifically mycosis fungoides (MF) and Sezáry syndrome (SS). In early clinical trials, the dose-limiting toxicity was stomatitis; the use of folic acid and vitamin B12 supplementation during pralatrexate therapy reduces this toxicity.

PTCL are a heterogeneous group of lymphoproliferative disorders arising from mature T-cells of post-thymic origin. PTCL represent a relatively uncommon group of hematologic malignancies within non-Hodgkin lymphomas (NHL), accounting for about 10% of NHL cases. Among PTCL cases worldwide, the most common subtypes include PTCL-not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), NK/T-cell lymphoma, adult T-cell leukemia/lymphoma (ATLL), ALK-positive anaplastic large cell lymphoma (ALCL), and ALK-negative ALCL; subtypes such as enteropathy-associated T-cell lymphoma (EATL) and primary cutaneous ALCL are relatively rare with ALCL more common than NK/T or ATLL in the United States. PTCLs are less responsive to and have less frequent durable remissions with standard chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and thus carry a poorer prognosis compared to diffuse large B-cell lymphomas. In prospective randomized studies, PTCLs have been included with aggressive B-cell lymphomas. However, due to small sample size, it has not been possible to assess the impact of chemotherapy in this subgroup and there have been no randomized studies comparing the chemotherapy regimens exclusively in persons with PTCL. The poor results with conventional chemotherapy have led many to explore the role of high-dose therapy followed by autologous stem cell rescue (HDT/ASCR) as a first-line consolidation therapy option. In persons with relapsed or refractory PTCL, several options are available. NCCN guidelines advocate second-line chemotherapy prior to transplant in relapsed persons and also support the use of second-line chemotherapy in subjects who are not candidates for transplant. Pralatrexate is a new antifolate with high affinity for reduced folate carrier type 1 (RFC-1), and has shown significant activity in persons with relapsed/refractory T-cell lymphoma and is considered an appropriate second-

line therapy option in individuals who are candidates for transplant, as well as though who are not eligible. In September 2009, pralatrexate became the first Food and Drug Administration (FDA)-approved single agent for the treatment of persons with relapsed or refractory PTCL. Results from the pivotal, international, phase II study (PROPEL) showed that pralatrexate resulted in an overall response rate (ORR) of 29% (complete response [CR] 11%; response assessed by an independent review) in pretreated subjects with relapsed or refractory PTCL (n=109 evaluable). Although treatment with pralatrexate resulted in an improvement in ORR, other clinical benefits such as improvement in progression-free survival or overall survival have not been demonstrated.

CTCL also represent a heterogeneous group of NHL characterized by an initial inflammation of the skin with clonally-derived malignant T lymphocytes. The diversity of clinical and pathologic manifestations among subsets of CTCL has led to much controversy over its diagnosis and classification and to the establishments of consensus guidelines by a joint effort of the World Health Organization and European Organization for Research and Treatment of Cancer (WHO-EORTC) in 2005. The two most common types of CTCL are MF, which is generally indolent in behavior, and SS, an aggressive leukemic form of the disease. Together, MF and SS comprise 54% of all CTCL. In 2007, NCCN created its first guideline on MF/SS. There are no sufficient randomized studies to recommend a preferred treatment strategy for MF/SS, nor do universally accepted treatment strategies exist. The chronicity of the disease results in many individuals being treated with multiple therapies in their lifetime, including: skin-directed therapies (e.g., ultraviolent light, topicals, and radiation), systemic agents ranging from retinoids to other biologics to chemotherapy, and an emerging role for allogeneic stem cell transplantation. Pralatrexate has also demonstrated activity in persons with CTCL. In a multicenter dose-finding study, pralatrexate 10 mg/m2 to 30 mg/m2 (administered weekly for 2 of 3 weeks or 3 of 4 weeks) was evaluated in persons with relapsed or refractory CTCL (n=54; MF, n=38 [70%]; SS, n=15 [28%]). Subjects had received a median of 4 prior systemic therapies (range, 1 to 11). The recommended dose identified was 15 mg/m2 weekly for 3 weeks of a 4 week cycle. The ORR for all evaluable subjects was 41% (CR in 5.5%). Thus, low-dose pralatrexate was shown to have high activity in persons with heavily pretreated CTCL. NCCN guidelines support the use of pralatrexate as second-line therapy in the treatment of MF/SS.

POSITION STATEMENT:

Initiation of pralatrexate (Folotyn) **meets the definition of medical necessity** for members meeting **ALL** of the following criteria:

1. Indication for use is treatment of **ANY** of the following
    a. Primary cutaneous anaplastic large cell lymphoma (ALCL)
    b. Mycosis Fungoides/Sezary Syndrome
    c. Hepatosplenic Gamma-Delta T-Cell Lymphoma
    d. Extranodal NK/T-Cell Lymphoma
    e. Peripheral T-cell lymphoma
    f. Adult T-cell leukemia/lymphoma
    g. Other FDA-approved or NCCN supported diagnosis (not previously listed above)

i. Member meets **ONE** of the following:

1. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)
2. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

2. Member is receiving **BOTH** of the following concomitantly:
    a. Vitamin B12 1 mg intramuscularly every 8 to 10 weeks
    b. Folic acid 1 to 1.25 mg orally once daily
3. Dose does not exceed 30 mg/m2 IV once weekly

Approval duration: 1 year

Continuation of pralatrexate (Folotyn) **meets the definition of medical necessity** for members meeting **ALL** of the following criteria:

1. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years, **OR** member has previously met all indication-specific initiation criteria
2. Member's disease has not progressed during treatment with pralatrexate
3. Member is receiving **BOTH** of the following concomitantly:
    a. Vitamin B12 1 mg intramuscularly every 8 to 10 weeks
    b. Folic acid 1 to 1.25 mg orally once daily
4. Dose does not exceed 30 mg/m2 IV once weekly

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING IT'S USAGE.

FDA-approved

- 30 mg/m2 administered as an intravenous push over 3 to 5 minutes once weekly for 6 weeks in 7-week cycles
- Prior to initiating, supplement with vitamin B12 1 mg intramuscularly every 8-10 weeks and folic acid 1.0-1.25 mg orally on a daily basis

Dose Adjustments

The management of severe or intolerable adverse reactions may require dose omission, reduction, or discontinuation of pralatrexate therapy. For dose modifications and omissions, refer to tables 1-3.

Table 1

Dose adjustments for mucositis		
Mucositis Grade† on Day of Treatment	**Action**	**Dose upon recovery to less than or equal to Grade 1 mucositis**
Grade 2	Omit dose	Continue prior dose
Grade 2 recurrence	Omit dose	20 mg/m^2
Grade 3	Omit dose	20 mg/m^2
Grade 4	Stop Therapy	
† Based on National Cancer Institute-Common Terminology Criteria for Adverse Events (refer to definition section)		

Table 2

Dose adjustments for hematologic toxicities			
Blood Count on Day of Treatment	**Duration of Toxicity**	**Action**	**Dose upon restart**
Platelets less than 50,000/mcL	1 week	Omit dose	Continue prior dose
	2 weeks	Omit dose	20 mg/m^2
	3 weeks	Stop therapy	--
ANC 500-1,000/mcL and NO fever	1 week	Omit dose	Continue prior dose
ANC 500-1,000/mcL with Fever Or ANC less than 500/mcL	1 week	Omit dose, give G-CSF or GM-CSF	Continue prior dose with G-CSF or GM-CSF
	2 weeks or recurrence		20 mg/m^2 with G-CSF or GM-CSF
	3 weeks or 2nd recurrence	Stop therapy	--
ANC, absolute neutrophil count; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte macrophage stimulating factor			

Table 3

Dose adjustments for all other treatment-related toxicities		
Toxicity Grade† on Day of Treatment	**Action**	**Dose upon recovery to less than or equal to Grade 2**
Grade 3	Omit dose	20 mg/m^2
Grade 4	Stop therapy	
†Based on National Cancer Institute-Common Terminology Criteria for Adverse Events (refer to definition section)		

Drug Availability

Sterile, single-use vials containing pralatrexate at a concentration of 20 mg/mL in the following presentations:

- 20 mg of pralatrexate in 1 mL solution in a vial (20 mg / 1 mL)
- 40 mg of pralatrexate in 2 mL solution in a vial (40 mg / 2 mL)

PRECAUTIONS:

Boxed Warning

None

Contraindications

None

Precautions/Warnings

- Thombocytopenia, neutropenia, and anemia: monitor blood counts and omit and/or reduce dose for hematologic toxicities.
- Mucositis: treatment with pralatrexate may cause mucositis. If ≥ Grade 2 mucositis is observed, dose should be modified. Monitor at least weekly.
- Dermatologic reactions: reactions, including fatal reactions, have occurred and may be progressive and increase in severity with further treatment. Monitor closely and omit and/or reduce dose or discontinue therapy.
- Tumor lysis syndrome: anticipate, monitor, and treat promptly.
- Hepatic toxicity: monitor for toxicity; refer to dosage/administration section for dose adjustments for toxicities.
- Renal toxicity: members with moderate to severe renal function impairment may be at greater risk for increased exposure and toxicity. Monitor renal function and for systemic toxicity; adjust accordingly. Avoid pralatrexate in those with end stage renal disease including those undergoing dialysis unless the potential benefit outweighs the risk.
- Pregnancy Category D: women should avoid becoming pregnant while being treated with pralatrexate.

BILLING/CODING INFORMATION:

HCPCS Coding:

J9307	Injection, pralatrexate, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity:

C84.00 – C84.09	Mycosis fungoides
C84.10 - C84.19	Sezary's disease
C84.40 – C84.49	Peripheral T-cell lymphoma, not classified
C84.60 – C84.79A	Anaplastic large cell lymphoma, ALK-positive & ALK-negative
C84.Z0 – C84.Z9	Other mature T/NK-cell lymphomas
C84.90 – C84.99	Mature T/NK-cell lymphomas, unspecified
C85.80 – C85.89	Other specified types of non-Hodgkin lymphoma
C86.00 – C86.60	Other specified types of T/NK-cell lymphomas
C91.50	Adult T-cell lymphoma/leukemia (HTLV-1-associated) not having achieved remission
C91.52	Adult T-cell lymphoma/leukemia (HTLV-1-associated) in relapse

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

DEFINITIONS:

Cancer: A term for diseases in which abnormal cells divide without control and can invade nearby tissues.

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)	
Grade	**Description**
1	Mild; asymptomatic or mild symptoms; clinical diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living
4	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event

Cutaneous T-cell lymphoma: any of a group of T-cell non-Hodgkin lymphoma that begins in the skin as an itchy, red rash that can thicken or form a tumor. The most common types are mycosis fungoides and Sezary syndrome.

Lymphoma: cancer that begins in cells of the immune system. There are two basic types: Hodgkin lymphoma and non-Hodgkin lymphoma.

Mucositis: inflammation of a mucous membrane.

Mycosis fungoides: A type of non-Hodgkin lymphoma that first appears on the skin and can spread to the lymph nodes or other organs such as the spleen, liver, or lungs

Non-Hodgkin Lymphoma: any of a large group of cancers of lymphocytes (white blood cells). The can be formed from either B-cells or T-cells. T-cell non-Hodgkin lymphomas include mycosis fungoides, anaplastic large cell lymphoma, and precursor T-lymphoblastic lymphoma. Lymphomas that occur after

bone marrow or stem cell transplantation are usually B-cell non-Hodgkin lymphomas. Prognosis and treatment depend on the stage and type of disease. Also called NHL.

Peripheral T-cell lymphoma: One of a group of aggressive (fast-growing) non-Hodgkin lymphomas that begins in mature T lymphocytes (T cells that have matured in the thymus gland and goes to other lymphatic sites in the body, including lymph nodes, bone marrow, and spleen.). Also called mature T-cell lymphoma.

Refractory: does not respond to treatment. The cancer may be resistant at the beginning of treatment or it may become resistant during treatment. Also called resistant cancer.

Relapse: The return of a disease or the signs and symptoms of a disease after a period of treatment.

Sezary syndrome: A cancer that affects the skin. It is a form of cutaneous T-cell lymphoma.

RELATED GUIDELINES:

Bexarotene (Targretin®) Capsules, 09-J1000-41

Granulocyte Colony Stimulating Factors, 09-J0000-62

Gemcitabine (Gemzar®) IV, 09-J0000-96

Vitamin B-12 Injections, 09-J0000-10

Vorinostat (Zolinza®) Capsules, 09-J1000-54

OTHER:

None applicable.

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 11/13/19.

GUIDELINE UPDATE INFORMATION:

03/15/10	New Medical Coverage Guideline.
01/01/11	Revision; consisting of updating coding.
02/15/11	Review and revision; consisting of updating coding and references.
03/15/12	Review and revision to guideline; consisting of dosage, coding and references.
03/15/13	Review and revision to guideline; consisting of revising/reformatting position statement to include treatment of cutaneous T-cell lymphomas and to require failure of previous chemotherapy; revised description section, dosage/administration, and precaution section; updated references; added pertinent definitions and related guidelines.
03/15/14	Review and revision to guideline; consisting of revising and reformatting position statement, dosage/administration, precautions/warning, and updating references.
11/01/15	Revision: ICD-9 Codes deleted.
10/01/16	Revision to guideline; consisting of updating ICD10 codes.
01/01/20	Revision to guidelines; addition of continuation criteria to position statement.
10/01/21	ICD 10 update.
10/01/24	ICD 10 update.