Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Denileukin diftitox-cxdl (Lymphir®)	MP-RX-FP-158-24	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of denileukin diftitox-cxdl (Lymphir®), an IL2-receptor-directed cytotoxin approved by the Food and Drug Administration (FDA) for the treatment of adult patients with relapsed or refractory Stage I-III cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy.

Background Information

Cutaneous T-Cell Lymphomas (CTCL) are a group of T cell lymphomas that primarily manifest in the skin, with no initial signs of extracutaneous disease. In early stages (IA, IB, and IIA), CTCL is typically managed with topical therapies and phototherapy. However, if the disease progresses despite these treatments, or if the patient is diagnosed at a more advanced stage, systemic treatments such as chemotherapy, retinoids, rexinoids, or biologic response modifiers are often required. As a result, patients may undergo a series of different treatments over time.

Denileukin diftitox is a recombinant fusion protein that merges interleukin-2 with diphtheria toxin. This agent specifically targets IL-2 receptors on the surface of cells, allowing diphtheria toxin fragments to enter and inhibit protein synthesis within the cells. Its unique mechanism of action not only targets malignant T-cells but also selectively depletes immunosuppressive regulatory T-cells (Tregs). Temporarily reducing Tregs can potentially enhance the patient's immune response against their tumors.

Denileukin diftitox-cxdl (Lymphir) received FDA approval based on results from the phase 3 Study 302 (NCT01871727). Study 302 was a multicenter, open-label trial that included patients aged 18 or older with relapsed or refractory stage I to IV cutaneous T-cell lymphoma (CTCL) who had at least 20% of their biopsied malignant cells expressing CD25, confirmed by immunohistochemistry. Enrolled patients had received a median of 4 prior lines of therapy (range, 1-18), involving both skin-directed and systemic treatments. Additional eligibility criteria included an ECOG performance status of 0-2, a life expectancy of at least 3 months, and sufficient bone marrow reserves. All patients received denileukin treatment until disease progression or the emergence of unacceptable toxicity. The study excluded patients with significant cardiac disease or uncontrolled infections.

The study was conducted in two parts: an initial lead-in phase aimed at determining the recommended dose of E7777 and dose-limiting toxicities, followed by the main phase focused on evaluating efficacy (ORR). The lead-in phase included 21 patients treated with doses ranging from 6 to 15 µg/kg/day. In the main study, 91 patients with stage I-IV CTCL received 9 µg/kg/day i.v. infusion on 5 consecutive days every 21 days.

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Efficacy was assessed in 71 patients with stage I-III persistent or recurrent CTCL from both study phases, with 69 included in the primary efficacy analysis. The results showed an ORR of 36.2% (95% CI, 25.0%-48.7%) in 25 of the 69 patients. An investigator-led analysis reported an ORR of 42.3% in 30 of the 71 patients (95% CI, 30.6%-54.6%). The median time to response was 1.41 months, with 52.0% of patients maintaining a response for at least 6 months. Additionally, 84.4% of skin-evaluable patients (n = 64) saw a reduction in skin tumor burden, and 12.5% achieved complete clearance of skin disease. Moreover, 31.7% of patients experienced significant improvement in pruritus.

Regarding safety, no cumulative toxicity was observed. Pooled safety data from 119 CTCL patients treated with 9 µg/kg of denileukin diftitox across three studies indicated that the most common adverse effects (occurring in at least 20% of patients) included elevated aminotransferases, decreased albumin, nausea, edema, reduced hemoglobin, fatigue, musculoskeletal pain, rash, chills, constipation, fever, and capillary leak syndrome (CLS). Denileukin diftitox carries a boxed warning for CLS, and patients should be closely monitored for its signs and symptoms, with treatment adjustments made as needed.

Denileukin diftitox-cxdl (Lymphir) has not yet been included in NCCN guidelines.

Approved Indications

Lymphir is approved by the FDA for the treatment of adult patients with relapsed or refractory Stage I-III cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy.

Other Uses

None

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Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J3490	Unclassified drugs
J9999	Not otherwise classified, antineoplastic drugs
C9399	Unclassified drugs

ICD-10	Description
C84.00-C84.09	Mycosis fungoide
C84.10-C84.19	Sézary disease
C84.A0-C84.A9	Cutaneous T-cell lymphoma, unspecified, different sites
Others	

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Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Denileukin diftitox-cxdl (Lymphir®)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

i. The individual has Stage I-III cutaneous T-cell lymphoma (CTCL), including Mycosis Fungoide and Sèzary Disease, that is relapsed or refractory; **AND**
ii. Tumor expresses CD25+, as confirmed by immunohistochemistry (at least 20% of T-cells expression); **AND**
iii. Individual has used at least one prior systemic therapy; **AND**
iv. Individual has an Eastern Cooperative Oncology Group ECOG status of 0-2.

B. Criteria For Continuation of Therapy

i. MMM considers continuation of denileukin diftitox-cxdl (Lymphir®) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of unacceptable toxicity or disease progression while on the current regimen. The following information should be submitted for reauthorization:
    A. A current oncology note documenting the patient's response to treatment showing no progression of disease.
    B. Current imaging studies and other objective measures, as appropriate, showing no progression of disease when compared with previous results.

C. Authorization Duration

i. Initial Approval Duration: Up to 6 months
ii. Reauthorization Approval Duration: Up to 6 months

D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. When the above criteria are not met, and for all other indications.

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Limits or Restrictions

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Drug	Recommended Dosing Schedule
Denileukin diftitox-cxdl (Lymphir®)	9 mcg/kg/day actual body weight administered as an intravenous infusion on Days 1 through 5 of a 21-day cycle until disease progression or unacceptable toxicity.
Exceptions	
None	

Reference Information

1. A trial of E7777 in persistent and recurrent cutaneous T-cell lymphoma. ClinicalTrials.gov. Accessed August 14, 2024. https://tinyurl.com/43722xwd
2. Citius Pharmaceuticals receives FDA approval for LYMPHIR™ (denileukin diftitox-cxdl) immunotherapy for the treatment of adults with relapsed or refractory cutaneous T-cell lymphoma. News release. Citius Pharmaceuticals, Inc. August 8, 2024. Accessed August 8. 2024. https://tinyurl.com/5xa5za9s
3. Kaminetzky D, Hymes KB. Denileukin diftitox for the treatment of cutaneous T-cell lymphoma. Biologics. 2008 Dec;2(4):717-24. doi: 10.2147/btt.s3084. PMID: 19707452; PMCID: PMC2727893.
4. Lymphir [package insert]. Cranford, NJ:Citius Pharmaceuticals, Inc.; August 2024.

Policy History

Revision Type	Summary of Changes	P&T Approval Date	MPCC Approval Date
Policy Inception	New Medical Policy creation.	9/16/2024	10/8/2024

Revised: 08/14/2024