Medical Policy

Utilization Management and Clinical Medical Policy

Policy Name:	Policy Number:	Scope:	Origination Date:	Effective Date:
Denileukin diftitox-cxdl (Lymphir®)	**MP-RX-FP-158-24**	☒ MMM MA ☒ MMM MultiHealth	**10/8/2024** **Last Review Date:** **7/22/2026**	**7/22/2026** **Frequently Revision:** **Annual**

Service Category:

- ☐ Anesthesia
- ☐ Surgery
- ☐ Radiology Procedures
- ☐ Pathology and Laboratory Procedures
- ☐ Medicine Services and Procedures
- ☐ Evaluation and Management Services
- ☐ DME/Prosthetics or Supplies
- ☒ Other: 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.

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

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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.

Lymphir has a black box warning for capillary leak syndrome (CLS), including life-threatening or fatal reactions. CLS was defined in the clinical trials as the occurrence of at least 2 of the following symptoms at any time during LYMPHIR therapy: hypotension, edema, and serum albumin <3 g/dL. These symptoms were not required to occur simultaneously to be characterized as CLS. It is recommended to regularly assess patients for weight gain, new onset or worsening of edema, dyspnea, and hypotension and monitor serum albumin levels prior to the initiation of each cycle of therapy and more often as clinically indicated. Withhold, reduce dose, or permanently discontinue based on severity. If Lymphir is withheld, resume treatment following resolution of CLS and when serum albumin is greater than or equal to 3 g/dL.

The National Comprehensive Cancer Network (NCCN) includes denileukin diftitox-cxdl (Lymphir) as a Category 2A recommended systemic therapy option for mycosis fungoides/Sézary syndrome. NCCN supports its use as primary or subsequent systemic therapy in selected patients with stage IB–IIA disease with extensive skin involvement, higher skin disease burden, predominantly plaque disease, blood involvement, or inadequate response to skin-directed therapy; stage IIB disease with limited tumor lesions, with or without local radiation therapy and/or skin-directed therapy; stage IIB disease with generalized tumor lesions in combination with skin-directed therapy; and stage III disease in combination with skin-directed therapy.

Approved Indications

A. 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

A. Lymphir (denileukin diftitox-cxdl) may be considered for use as primary or subsequent systemic therapy for mycosis fungoides/Sézary syndrome in accordance with NCCN Category 2A recommendations, including selected patients with stage IB–IIA, stage IIB, or stage III disease when systemic therapy is clinically appropriate.

Policy Name:	Policy Number:	Scope:	Origination Date:	Effective Date:
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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.

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.)*

Requests for Lymphir (denileukin diftitox-cxdl) may be approved if the following criteria are met:

i. Individual has a diagnosis of cutaneous T-cell lymphoma (CTCL); **AND**
ii. Biopsied malignant cells have expression of CD25 on at least 20% of cells, as confirmed by immunohistochemistry; **AND**
iii. Individual meets one of the following:
    A. Individual has relapsed or refractory Stage I-III CTCL after at least one prior systemic therapy (Label); **OR**
    B. Individual is using as primary or subsequent systemic therapy for mycosis fungoides/Sézary syndrome in accordance with NCCN 2A recommendations and meets *one* of the following (NCCN 2A):
        1. Individual has stage IB-IIA mycosis fungoides (MF) and has extensive skin involvement, higher skin burden, predominately plaque disease burden, blood involvement, or inadequate response to skin-directed therapy in combination with skin directed therapy; **OR**
        2. Individual has stage IIB MF with limited tumor lesions, with or without local radiation therapy and with or without skin-directed therapy; **OR**
        3. Individual has stage IIB MF with generalized tumor lesions in combination with skin-directed therapy; **OR**
        4. Individual has stage III MF in combination with skin-directed therapy.

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:

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			Last Review Date: 7/22/2026	Frequently Revision: Annual

A. A current oncology note documenting the patient's response to treatment or stable disease and absence of unacceptable toxicity including clinically significant capillary leak syndrome, visual impairment, infusion-related reactions, or hepatotoxicity; **AND**

B. Current objective disease assessment(s), as appropriate, such as skin examination, skin disease assessment, laboratory results, imaging studies, and/or other objective measures, as appropriate, showing no progression of disease when compared with previous results; **AND**

C. Documentation that serum albumin, hepatic function, and renal function have been assessed prior to the current treatment cycle, as clinically appropriate.

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®) injection 300 mcg single-dose vial	• 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	
• Assess hepatic and renal function prior to starting each treatment cycle. • Delay administration if serum albumin is less than 3 g/dL until serum albumin is greater than or equal to 3 g/dL. • Monitor liver enzymes and bilirubin at baseline and during treatment as clinically indicated.	

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Codes Information:

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.

ICD-10 Diagnostic Codes:

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

HCPCS Codes:

Codes	Description
J9161	Injection, denileukin diftitox-cxdl, 1 mcg

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. Foss, Francine M et al. "Efficacy and Safety of Denileukin Diftitox-Cxdl, an Improved Purity Formulation of Denileukin Diftitox, in Patients With Relapsed or Refractory Cutaneous T-Cell Lymphoma." Journal of clinical oncology : official journal of the American Society of Clinical Oncology vol. 43,10 (2025): 1198-1209. doi:10.1200/JCO-24-01549
5. Citius Oncology, Inc. (2024). *Lymphir™ (denileukin diftitox-cxdl) for injection, for intravenous use: Prescribing information*. Revised August 2024. Accessed May 14, 2026.
6. NCCN Clinical Practice Guidelines in Oncology™. © 2025 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. a.
    a. Cutaneous Lymphomas. V2.2026. Revised February 13, 2026.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

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Policy History:

Type of Review	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Annual Review	Updated Background Information to include the boxed warning for capillary leak syndrome and NCCN recommendations. Updated clinical criteria to align with NCCN recommendations, removed ECOG performance status criteria, and revised continuation of therapy criteria to address disease progression and unacceptable toxicity. Updated the quantity limitations table to align with prescribing information dosing, administration considerations, and safety precautions, including serum albumin and hepatic monitoring requirements. Coding reviewed: no changes. Wording and formatting changes were made, and the new policy template was incorporated.	7/13/2026	7/22/2026
Annual Review	Minimal changes; Word Formatting. Coding Update: Removed HCPCS NOC J9999, C9399. Added HCPCS J9161 effective 4/1/25.	8/25/2025	9/8/2025
Policy Inception	New Medical Policy creation.	9/16/2024	10/8/2024