Medical Drug Clinical Criteria

Subject:	Lymphir (denileukin diftitox-cxdl)		
Document #:	CC-0268	**Publish Date:**	~~12/11/2024~~10/01/2025
Status:	Revised	**Last Review Date:**	~~11/15/2024~~08/15/2025

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Overview

This document addresses the use of Lymphir (denileukin diftitox-cxdl). Lymphir is an IL2-receptor-directed cytotoxin indicated 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. Denileukin diftitox was previously approved under the brand name Ontak but was withdrawn from the market in 2014 due to production issues.

The approval of Lymphir is based on results from the Phase 3 Pivotal Study 302 (NCT01871727) of CTCL patients who had previously received at least one systemic treatment. Eligible patients were required to have expression of CD25 on ≥ 20% of biopsied malignant cells by immunohistochemistry. The study excluded patients with significant cardiac disease or uncontrolled infections. Actual study patients received a median of 4 (min, max: 1, 18) prior anticancer therapies. The primary efficacy population includes 69 patients with stage I-III CTCL who were treated with denileukin diftitox-cxdl (9 µg /kg/day). The primary efficacy outcome measure was Objective Response Rate (ORR), as assessed by an Independent Review Committee (IRC). The ORR was 36.2%, (95% CI: 25.0-48.7), with 8.7% achieving a Complete Response (CR). The National Comprehensive Cancer Network (NCCN) states that mycosis fungoides is the most common cutaneous T-cell lymphoma (CTCL).

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.

Clinical Criteria

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.

Lymphir (denileukin diftitox-cxdl)

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. Individual has relapsed or refractory disease after at least one prior systemic therapy; **AND**~~
~~III.~~II. Individual has stage I to III disease; **AND**
III. Biopsied malignant cells have expression of CD25 on at least 20% of cells; **AND**
IV. Individual has relapsed or refractory disease after at least one prior systemic therapy; **OR**
V. Individual meets one of the following (NCCN 2A):

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A. Individual is using as primary systemic treatment for stage IB-IIA mycosis fungoides (MF) and has extensive skin involvement, higher skin burden, predominately plaque disease burden, predominantly plaque disease, blood involvement, or inadequate response to skin-directed therapy; **OR**

B. Individual is using as primary systemic treatment for stage IIB MF with limited tumor lesions, with or without local radiation therapy and with or without skin-directed therapy; **OR**

C. Individual is using as primary systemic treatment for stage IIB MF with generalized tumor lesions in combination with skin-directed therapy; **OR**

~~IV.~~D. Individual is using as primary systemic treatment for stage III MF with skin-directed therapy.

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Lymphir (denileukin diftitox-cxdl) may not approve if all indications above are not met and for all other indications.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J9161	Injection, denileukin diftitox-cxdl, 1 mcg [Lymphir]

ICD-10 Diagnosis

C84.00-C84.09	Mycosis fungoides
C84.10-C84.19	Sezary disease

Document History

Revised: 08/15/2025
Document History:

- 08/15/2025 – Annual Review: Add primary treatment for mycosis fungoides. Coding Reviewed: No changes.
- 03/04/2025 – Coding Update: Removed HCPCS NOC J9999, C9399 and all diagnosis pend for Lymphir. Added HCPCS J9161 effective 4/1/25. Added ICD-10-CM C84.00-C84.09 and C84.10-C84.19.
- 11/15/2024 – Select Review: Add standard do not approve language. Coding Reviewed: No changes.
- 09/09/2024 – Annual Review: New criteria for Lymphir. Coding Reviewed: Add HCPCS J9999 and C9399 for Lymphir. All diagnosis pend for NOC codes.

References

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Updated periodically.
2. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
3. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc. Updated periodically.
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. 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. Primary Cutaneous Lymphomas. V2.2025. Revised April 1, 2025.

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.