Denileukin Diftitox-cxdl (LYMPHIR) for IV Injection
National Drug Monograph
May 2026
VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: AC, active-controlled; CO, crossover; DB, double-blind; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; MC, multicenter; MN, multinational; PC, placebo-controlled; Q, GRADE quality of evidence; RCT, randomized clinical trial

FDA PRESCRIBING INFORMATION[1]	
Description / MOA	Denileukin diftitox-cxdl (DD-cxdl), an immunotherapy designated an orphan drug by the FDA, is the first treatment for cutaneous T-cell lymphoma that targets the IL-2 receptor (IL-2R). DD-cxdl is an engineered fusion protein comprised of human interleukin-2 (IL-2) and diphtheria toxin (DT) that kills tumor cells directly. Binding of the drug to cell-surface IL-2Rs results in internalization of DD-cxdl into the cell, cleavage, then release of DT. DT inhibits protein synthesis, causing cell death. Both malignant T-cells and immunosuppressive regulatory T-cells (Tregs) express IL-2Rs and are targeted. The transient depletion of Tregs increases the body's immune response against cancer cells. DD-cxdl is a purer formulation of denileukin diftitox (DD; ONTAK by Eisai Inc.), a product approved under accelerated approval in 1999 and under regular approval in 2008. Although it is an active listing on the FDA web site (with action last recorded on 2/10/2020), DD was voluntarily withdrawn from the US market in 2014 because of manufacturing problems related to bacterial expression and purification. Developed using a refined production process, DD-cxdl has a higher percentage of protein monomer species and lower levels of misfolded protein and protein aggregates, with 1.5–2 times greater specificity in non-clinical assays than DD.[2]
Indication Under Review & CTCL Staging	Treatment of adults with relapsed or refractory (R/R) stage I–III cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy. TNMB Staging System for CTCL is characterized by 4 sites: skin (T), lymph nodes (N), blood (B), visceral organs (M) **Stages IA-IIA (early stage)** IA: patches/plaques < 10% BSA, no nodal, visceral or blood component IB: patches/plaques ≥ 10% BSA, no extracutaneous disease IIA: patches/plaques + N1-2 lymph nodes **Stages IIB-IV (advanced)** IIB: tumors (≥ 1 cm) with/without N1-2 nodes IIIA: erythroderma (≥ 80% BSA) w/o blood involvement IIIB: erythroderma with low blood burden (B1) IVA1: high blood burden (B2) = Sezary Syndrome IVA2: N3 lymph node involvement IVB: visceral involvement, M1a (bone marrow only) or M1b (visceral organs)
Dosage Regimen	DD-cxdl 9 mcg/kg/day actual body weight IV over 60 minutes on Days 1 through 5 of a 21-day treatment cycle. Administer DD-cxdl until disease progression or unacceptable toxicity.
Dosage Modifications	Dosage modifications are required for capillary leak syndrome, visual impairment, infusion-related reactions, hepatotoxicity, and other adverse reactions. Refer to the USPI for details.
Dosage Form/Storage	For IV injection: 300 mcg/vial containing lyophilized cake for reconstitution and further dilution. Should be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) and should not be frozen.

EFFICACY CONSIDERATIONS	
Trial	**Efficacy and Safety of Denileukin Diftitox-cxdl, an Improved Purity Formulation of Denileukin Diftitox, in Patients With Relapsed or Refractory Cutaneous T-Cell Lymphoma[3]**
Design	Phase III, US and AU, multicenter, open-label, single-arm, observational study consisting of a lead-in study (to establish the MTD) and the main study. *Primary Efficacy End Point (analyzed in patients with stage IA–IIIB CTCL to align with the historical reference study of DD[4])*: Objective response rate (ORR) for regression of measurable disease using Global Response Score.
Population/ Demographics	*Entry Criteria*: CD25-positive, histopathologically confirmed CTCL [mycosis fungoides (MF) and/or Sézary syndrome (SS)]; ECOG performance status of 0 or 1 and ≥ 1 prior systemic therapy; stage IA–IVA CTCL excluding visceral disease *Primary efficacy analysis set (PEAS)*: 69 patients who had stage IA–IIIB CTCL. *Baseline Characteristics, PEAS*: Median age 64 years (28-87); 65.2% male; 72.5% White; ECOG performance status 0–1; MF 95.7%; SS 4.3%; Stage IA/IB/IIA (early stage) 43.5%; stage IIB (tumor +/- LN) 34.8%; stage IIIA/IIIB (erythroderma, +/- blood) 21.7%; Median number of anticancer therapies 4 (range, 1–18; mode 5–7); photodynamic therapy 56.5%; total skin electron beam therapy (TSEBT) 42.0%; topical chemotherapy 29.0%, local radiation 27.5%; allogeneic stem-cell transplantation (ASCT) 1.4%; retinoid 49.3%; methotrexate/pralatrexate 49.3%; histone deacetylase (HDAC) inhibitor 34.8%; interferon 33.3%; brentuximab vedotin 26.1%; other immunotherapy 20.3%; other systemic chemotherapy 17.4%; mogamulizumab 11.6%; investigational anticancer therapy 18.8%; other anticancer therapy 10.1%.
Intervention	Lead-in Study: 9 µg/kg once daily for 5 days was selected as the acceptable safe dose to use in the main study. DD-cxdl 9 µg/kg/d IV once daily for 5 days every 21 days for up to 8 cycles (24 weeks, main study). Patients who showed clinical benefit could continue therapy (20 patients continued beyond 24 weeks for as many as ~125 weeks).
Premedications	All patients received acetaminophen, diphenhydramine, antiemetic agents, and hydration about 30 minutes before each DD-cxdl infusion in cycles 1–3. Premedication was optional from cycle 4 on.
Results	**Tumor Response** **End Point** / **DD-cxdl** Complete Response Rate, n/N (%) — 6/69 (8.7) ORR (CR + PR), n/N (%) — 25/69 (36.2) Median KM Duration of Response, mos (N = 25) — 8.9 Median Observed Duration of Response, mos (N = 25) — 6.5 ≥ 6 months — 13/25 (52.0) ≥ 12 months — 5/25 (20.0) Median Time to Response, mos — 1.4 (0.7, 2.1) Complete Clearance of Skin Disease, n/N (%) — (12.5%) ≥ 50% Reduction in Skin Tumor Burden, n/N (%) — (48.4) KM, Kaplan-Meier Median number of cycles received: 6, range 1-42
Authors' & FDA Conclusions	The results showed that DD-cxdl would potentially fill an unmet medical need for patients with R/R CTCL; per FDA medical review, DD-cxdl has clinically meaningful activity in patients with relapsed or refractory CTCL.

SAFETY CONSIDERATIONS	
Boxed Warnings	*Capillary leak syndrome (CLS)*, potentially life-threatening or fatal CLS defined as ≥ 2 of the following at any time during therapy: hypotension, edema, serum albumin < 3g/dL Occurred in 27% of pooled population (Gr 3 85; one fatality); Majority occurred w/in first 2 cycles; onset ~6.5 days; median duration 14 days Assess patients regularly for weight gain, new onset/worsening edema, dyspnea, hypotension; Monitor serum albumin prior to each cycle and as clinically indicated
Contraindications	None
Other Warnings	*Visual impairment* (9% of patients overall; 8% Grade 1; 1% Grade 2) *Infusion-related reactions* (69% of patients overall; 3.4% Grade 3; 83% of cases occurred in Cycles 1 and 2) *Hepatotoxicity* – Elevated ALT (70% of patients overall; 22% Grade 3) and AST (64% overall; 9% Grade 3). Grade 3 events had a median onset of 8 days (range, 1–15 days) and median time to resolution of 15 days (range, 7–50 days). Elevated total bilirubin (5% overall; 0.9% Grade 3). *Embryofetal toxicity*
Top 5 AEs (≥ 20%)	Increased transaminases, decreased albumin, nausea, edema, decreased hemoglobin
Drug Interactions	None reported.
Trial Safety Results	*Deaths*: Not reported. *Serious Adverse Events (SAEs)*: 38% of patients, most commonly (> 2%) capillary leak syndrome (10%), infusion-related reactions (9%), sepsis (7%), skin infection (2.9%), pyrexia (2.9%), and rash (2.9%). *Discontinuations Due to Adverse Events (DAEs)*: 12% of patients, most commonly due to capillary leak syndrome, infusion-related reaction, renal insufficiency, respiratory failure, and sepsis. *Dosage Interruptions Due to Adverse Events*: 38% of patients, most commonly due to capillary leak syndrome, infusion-related reaction, weight increase, nausea, and tachycardia. *Most Common Adverse Events*: Infusion reaction (73.9%), hypersensitivity (68.1%), hepatotoxicity (36.2%), capillary leak syndrome (grade ≥3, 5.8%), nausea (43.5%), fatigue (31.9%)

THERAPEUTIC ALTERNATIVES AND THEIR PLACE IN THERAPY FOR CTCL R/R AND MULTIPLE PRIOR THERAPIES

DRUG	On VANF	CFU	FDA	Study design/ pop'n	Endpoints	
Denileukin diftitox-cxdl	TBD	TBD	Treatment of adults with R/R stage I–III CTCL after ≥ 1 LOT	Phase 3, single-arm N=69 Stage IA-IIIB, ≥ 1 LOT Median 4 LOT	**ORR 36.2%** CR 8.7% ORR4 ≥ 6 mos mDOR 8.9 mos mPFS 4.4 mos CLS 27%	Requires monitoring for CLS **NCCN recs** IB-IIA MF: useful IIB tumor MF: preferred III erythrodermic MF: useful
Brentuximab	Yes, PA-F	Restrict to h/o	Treatment of CD30 MF after prior systemic therapy	Phase 3 vs. methotrexate or bexarotene x48 wks N=64 CD30+ MF or pcALCL; SS excluded Median 2 LOT	**ORR4 56.3 vs. 13%** CR 17 vs. 2% mDOR not reached mPFS 17 vs. 3.5 mos PN 44 vs. 6%	Preferred in skin, LN, visceral disease, MF-LCT **NCCN recs** IB-IIA MF: preferred IIB tumor MF: preferred III erythrodermic MF: preferred SS: other rec IVB visceral: preferred
				Phase 2 N=48 CD30+ CTCL	ORR 73% CR 35% mDOR 32 weeks mPFS not reported	Responses independent of CD30 expression; activity noted with <10% CD30
Mogamulizumab	No	CFU		Phase 3 vs. vorinostat MF or SS;	ORR 28 vs. 5% CR 5 vs. 0% mDOR 14.1 mos	Responses higher in stage III/IV with blood involvement:

DRUG	On VANF	CFU	FDA	Study design/ pop'n	Endpoints	
				MF-LCT excluded Median 3 LOT	**mPFS 7.6 vs. 3 mos**	37 vs. 3%
					Rash 20%	Preferred in SS or blood involved disease
						NCCN recs IIB tumor MF: preferred III erythrodermic MF: preferred SS: preferred IVB visceral: other

ORR4 Overall Response Rate lasting $\geq$ 4 months, OS Overall Survival; SS Sézary syndrome; MF mycosis fungoides; MF-LCT mycosis fungoides with large cell transformation; LOT line of therapy; mPFS median progression-free survival; mDOR median duration of response; CR complete response; CLS capillary leak syndrome; pcALCL primary cutaneous anaplastic large-cell lymphoma

POTENTIAL PLACE IN THERAPY OF Denileukin Diftitox-cxdl

- CTCL is characterized by clonal overgrowth of malignant T cells that primarily impact the skin. Mycosis Fungoides (MF) is the most common subtype (60-80% cases) while Sezary Syndrome (SS) is a rare leukemic variant impacting < 5-10% of cases. MF is notable for patches, plaques and tumors while SS is notable for blood involvement, erythroderma and lymphadenopathy.
- Treatment for CTCL varies upon disease compartment and variable drug effect. Clinical trial data helps to discern disease characteristics and drug activity. For example, ALCANZA (brentuximab) did not include the SS population, whereas MAVORIC (mogamulizumab) included patients with MF or SS. In patients with SS or high blood burden, mogamulizumab is preferred. Patients with MF-LCT were excluded from MAVORIC, therefore brentuximab would be preferred in this setting. Brentuximab also demonstrated efficacy in disease affecting skin, lymph nodes and viscera.
- Goals of therapy include response to minimize progression and control symptoms. Hematopoietic stem cell transplant is the only treatment with curative intent, to date.
- DD was not studied in a comparative study design and was not studied in the SS population. It was effective in a heavily pretreated population that also included brentuximab (26%) and mogamulizumab (12%).
- DD has a unique toxicity profile that requires monitoring at baseline and throughout the course of therapy (i.e. capillary leak syndrome, ocular toxicity, infusion-related reactions, hepatotoxicity). A boxed warning highlights the risk of capillary leak syndrome.

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