Evolent Clinical Guideline 3150 for Epkinly™ (epcoritamab-bysp)

Guideline Number:	Applicable Codes	
Evolent_CG_3150		
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Original Date:	**Last Revised Date:**	**Implementation Date:**
July 2023	July 2026	July 2026

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STATEMENT

Purpose

To define and describe the accepted indications for Epkinly (epcoritamab-bysp) usage in the treatment of cancer, including FDA approved indications, and off-label indications.

Evolent is responsible for processing all medication requests from network ordering providers. Medications not authorized by Evolent may be deemed as not approvable and therefore not reimbursable.

The use of this drug must be supported by one of the following: FDA approved product labeling, CMS-approved compendia, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) clinical guidelines, or peer-reviewed literature that meets the requirements of the CMS Medicare Benefit Policy Manual Chapter 15.

INDICATIONS

Continuation requests for a not-approvable medication shall be exempt from this Evolent policy provided

- The member has not experienced disease progression on the requested medication AND
- The requested medication was used within the last year without a lapse of more than 30 days of having an active authorization AND
- Additional medication(s) are not being added to the continuation request.

Diffuse Large B-Cell Lymphoma (DLBCL)

- Epkinly (epcoritamab-bysp) may be used in adult members as monotherapy for relapsed or refractory DLBCL, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma AND the member has failed at least two systemic therapies, including an anti-CD20 monoclonal antibody (e.g., R-CHOP, R-ICE, R-DHAP, R-ESHAP, R-EPOCH, R-GDP).
- Epkinly (epcoritamab-bysp) may be used in combination with gemcitabine and oxaliplatin in adult members for the treatment of relapsed or refractory DLBCL after failure of at least one line of systemic therapy, AND the member is not a candidate for CAR-T therapy or transplant.

Follicular Lymphoma

- Epkinly (epcoritamab-bysp) may be used in combination with Revlimid (lenalidomide) and rituximab/rituximab biosimilar in adult members for the treatment of relapsed or refractory follicular lymphoma after at least one line of systemic therapy.

- Epkinly (epcoritamab-bysp) may be used in adult members as monotherapy for relapsed or refractory follicular lymphoma AND the member has failed at least two systemic therapies.

CONTRAINDICATIONS/WARNINGS

- US Boxed Warning
  - Cytokine release syndrome (CRS), including serious or life-threatening reactions, can occur in patients receiving epcoritamab. Initiate treatment with the epcoritamab step-up dosage schedule to reduce the incidence and severity of CRS. Withhold epcoritamab until CRS resolves or permanently discontinue based on severity.
  - Immune effector cell-associated neurotoxicity syndrome (ICANS), including life-threatening and fatal reactions, can occur with epcoritamab. Monitor patients for neurological signs or symptoms of ICANS during treatment. Withhold epcoritamab until ICANS resolves or permanently discontinue based on severity.

EXCLUSION CRITERIA

- Disease progression while taking Epkinly (epcoritamab-bysp).
- Dosing exceeds single dose limit of Epkinly (epcoritamab-bysp) 48 mg.
- Investigational use of Epkinly (epcoritamab-bysp) with an off-label indication that is not sufficient in evidence or is not generally accepted by the medical community. Sufficient evidence that is not supported by CMS recognized compendia or acceptable peer reviewed literature is defined as any of the following:
  - Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
  - Whether the administered chemotherapy/biologic therapy/immune therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.
  - Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients. Generally, the definitions of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of less than 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.
  - Whether the experimental design, considering the drugs and conditions under investigation, is appropriate to address the investigative question. (For example, in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover).
  - That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
  - That case reports are generally considered uncontrolled and anecdotal information

and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.

- That abstracts (including meeting abstracts) without the full article from the approved peer-reviewed journals lack supporting clinical evidence for determining accepted uses of drugs.

CODING AND STANDARDS

Codes

- J9321 - Injection, epcoritamab-bysp, 0.16 mg

Applicable Lines of Business

☐	CHIP (Children's Health Insurance Program)
☒	Commercial
☒	Exchange/Marketplace
☒	Medicaid
☐	Medicare Advantage

POLICY HISTORY

Date	Summary
July 2026	• Updated DLBCL indication • Updated references
December 2025	• Updated DLBCL and Follicular Lymphoma indications • Updated exclusion criteria • Updated references
July 2025	• Converted to new Evolent guideline template • This guideline replaces UM ONC_1479 Epkinly (epcoritamab-bysp) • Updated references

Date	Summary
July 2024	• Added follicular lymphoma indication section based on new FDA label expansion (June 2024) • Added new references • Updated NCH verbiage to Evolent

LEGAL AND COMPLIANCE

Guideline Approval

Committee

Reviewed / Approved by Evolent Specialty Services Clinical Guideline Review Committee

Disclaimer

Evolent Clinical Guidelines do not constitute medical advice. Treating health care professionals are solely responsible for diagnosis, treatment, and medical advice. Evolent uses Clinical Guidelines in accordance with its contractual obligations to provide utilization management. Coverage for services varies for individual members according to the terms of their health care coverage or government program. Individual members' health care coverage may not utilize some Evolent Clinical Guidelines. Evolent clinical guidelines contain guidance that requires prior authorization and service limitations. A list of procedure codes, services or drugs may not be all inclusive and does not imply that a service or drug is a covered or non-covered service or drug. Evolent reserves the right to review and update this Clinical Guideline in its sole discretion. Notice of any changes shall be provided as required by applicable provider agreements and laws or regulations. Members should contact their Plan customer service representative for specific coverage information.

REFERENCES

1. Brody JD, et al. Epcoritamab plus GemOx in transplant-ineligible relapsed/refractory DLBCL: results from the EPCORE NHL-2 trial. *Blood*. 2025 Apr 10;145(15):1621-1631. doi: 10.1182/blood.2024026830.
2. Falchi L, et al. Fixed-duration epcoritamab plus R2 drives favorable outcomes in relapsed or refractory follicular lymphoma. *Blood*. 2025 Nov 27;146(22):2629-2640. doi: 10.1182/blood.2025029909.
3. Hutchings M, et al. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. *Lancet*. 2021 Sep 25;398(10306):1157-1169. doi: 10.1016/S0140-6736(21)00889-8.
4. Linton KM. et al. Epcoritamab monotherapy in patients with relapsed or refractory follicular lymphoma (EPCORE NHL-1): a phase 2 cohort of a single-arm, multicentre study. *Lancet Haematol*. 2024 Aug;11(8):e593-e605. doi: 10.1016/S2352-3026(24)00166-2.
5. Epkinly prescribing information. Genmab US, Inc. Plainsboro, NJ 2026.
6. Clinical Pharmacology Elsevier Gold Standard 2026.
7. Micromedex® Healthcare Series: Micromedex Drugdex Ann Arbor, Michigan 2026.
8. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium 2026.
9. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD 2026.
10. Ellis LM, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol*. 2014 Apr 20;32(12):1277-80.
11. Medicare Benefit Policy Manual Chapter 15 Covered Medical and Other Health Services: **https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf**.
12. Current and Resolved Drug Shortages and Discontinuations Reported to the FDA: **http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm**.