Clinical Policy: Epcoritamab-bysp (Epkinly)

Reference Number: CP.PHAR.634
Effective Date: 09.01.23
Last Review Date: 08.26
Line of Business: Commercial, HIM/ICHRA, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Epcoritamab-bysp (Epkinly™) is a bispecific CD20-directed CD3 T-cell engager.

FDA Approved Indication(s)

Epkinly is indicated:

- For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after two or more lines of systemic therapy.*
- In combination with lenalidomide and rituximab for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL)
- As monotherapy for the treatment of adult patients with relapsed or refractory FL after two or more lines of systemic therapy.

*This indication is approved under accelerated approval based on response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Policy/Criteria

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

It is the policy of health plans affiliated with Centene Corporation® that Epkinly is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. B-Cell Lymphomas (must meet all)**:**

1. Diagnosis of one of the following (a, b, c, d, or e):
   a. DLBCL (*see subtypes in Appendix D*);
   b. Classic FL (grades 1, 2 and 3A);
   c. Histologic transformation of follicular or marginal zone lymphoma to DLBCL (off-label);
   d. HIV-related B-cell lymphomas (off-label);
   e. Post-transplant lymphoproliferative disorders (off-label);
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Member has received ≥ 1 line of systemic therapy (*see Appendix B*), and one of the following (a, b, or c):

a. For any indication: Prescribed as monotherapy, and member has both of the following (i and ii):
   i. Partial response, no response, progressive, relapsed, or refractory disease following prior systemic therapy;
   ii. One of the following (1 or 2):
      1) Member has received ≥ 2 lines of systemic therapy (*see Appendix B*);
      2) Request is for DLBCL arising from chronic lymphocytic leukemia (CLL) (Richter transformation);
b. For DLBCL, HIV-related B-cell lymphomas, and post-transplant lymphoproliferative disorders: Prescribed in combination with GemOx (gemcitabine and oxaliplatin) AND member has one of the following (i, ii, or iii):
   i. Relapsed or refractory disease;
   ii. Relapsed disease < 12 months after completion of first-line therapy or primary refractory disease in non-candidates for CAR T-cell therapy (includes patients who do not have access to CAR T-cell therapy);
   iii. Relapsed disease > 12 months after completion of first-line therapy if no intention to proceed to transplant;
c. For classic FL: Prescribed in combination with lenalidomide and rituximab for relapsed or refractory disease;*
   **Prior authorization may be required for lenalidomide and rituximab*

5. Request meets one of the following (a or b):*
   a. All of the following (i, ii, and iii):
      i. Cycle 1 step-up doses: Dose does not exceed all the following (1, 2, 3, and 4):
         1) 0.16 mg on day 1;
         2) 0.8 mg on day 8;
         3) For FL: 3 mg on day 15;
         4) Three 4 mg/0.8 mL vials;
      ii. 48 mg per dose (one 48 mg vial; see *Section V* below for details on dosing schedule by cycle);
      iii. If prescribed in combination with lenalidomide and rituximab for FL, treatment does not exceed a total of 12 cycles;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM/ICHRA – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace/ICHRA, and CP.PMN.255 for Medicaid; or

b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace/ICHRA, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace/ICHRA, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. B-Cell Lymphomas (must meet all)**:**

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Epkinly for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If prescribed in combination with lenalidomide and rituximab for FL, treatment does not exceed a total of 12 cycles;
4. If request is for a dose increase, request meets one of the following (a or b):*
   a. New dose does not exceed 48 mg per dose (one 48 mg vial; see *Section V* below for details on dosing schedule by cycle);
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM/ICHRA – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace/ICHRA, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace/ICHRA, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace/ICHRA, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace/ICHRA, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CLL: chronic lymphocytic leukemia
DLBCL: diffuse large B-cell lymphoma
FDA: Food and Drug Administration
FL: follicular lymphoma

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
DLBCL: Examples of First-Line Treatment Regimens		
RCHOP (Rituxan® (rituximab), cyclophosphamide, doxorubicin, vincristine, prednisone)	Varies	Varies
RCEPP (Rituxan® (rituximab), cyclophosphamide, etoposide, prednisone, procarbazine)	Varies	Varies
RCDOP (Rituxan® (rituximab), cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)	Varies	Varies
DA-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicine) + Rituxan® (rituximab)	Varies	Varies
RCEOP (Rituxan® (rituximab), cyclophosphamide, etoposide, vincristine, prednisone)	Varies	Varies
RGCVP (Rituxan®, gemcitabine, cyclophosphamide, vincristine, prednisone)	Varies	Varies
Pola-R-CHP (Polivy™ (polatuzumab vedotin-piiq), rituximab, cyclophosphamide, doxorubicin, prednisone)	Varies	Varies
DLBCL: Examples of Second-Line Treatment Regimens		
Bendeka® (bendamustine) ± Rituxan® (rituximab)	Varies	Varies
CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± Rituxan® (rituximab)	Varies	Varies
CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± Rituxan® (rituximab)	Varies	Varies
DA-EPOCH ± Rituxan® (rituximab)	Varies	Varies
GDP (gemcitabine, dexamethasone, cisplatin) ± Rituxan® (rituximab)	Varies	Varies
gemcitabine, dexamethasone, carboplatin ± Rituxan® (rituximab)	Varies	Varies
GemOx (gemcitabine, oxaliplatin) ± Rituxan® (rituximab)	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
gemcitabine, vinorelbine ± Rituxan® (rituximab)	Varies	Varies
lenalidomide ± Rituxan® (rituximab)	Varies	Varies
Rituxan® (rituximab)	Varies	Varies
DHAP (dexamethasone, cisplatin, cytarabine) ± Rituxan® (rituximab)	Varies	Varies
DHAX (dexamethasone, cytarabine, oxaliplatin) ± Rituxan® (rituximab)	Varies	Varies
ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± Rituxan® (rituximab)	Varies	Varies
ICE (ifosfamide, carboplatin, etoposide) ± Rituxan® (rituximab)	Varies	Varies
MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± Rituxan® (rituximab)	Varies	Varies
FL: Examples of First-Line and Second-Line Treatment Regimens		
Examples of first-line, second-line and subsequent therapies: • bendamustine + obinutuzumab or rituximab • CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + obinutuzumab or rituximab • CVP (cyclophosphamide, vincristine, prednisone) + obinutuzumab or rituximab • Lenalidomide + rituximab *Single-agent examples*: rituximab; Leukeran® (chlorambucil) ± rituximab; cyclophosphamide ± rituximab; Revlimid® (lenalidomide) ± rituximab	Varies	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): none reported
- Boxed warning(s): cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome

Appendix D: DLBCL Subtypes per the National Comprehensive Cancer Network (NCCN)

- DLBCL, NOS (FDA-approved use)
- DLBCL arising from follicular lymphoma or marginal zone lymphoma
- Primary DLBCL of the CNS
- DLBCL arising from CLL (Richter transformation)
- Follicular lymphoma grade 3B/follicular LBCL
- Intravascular LBCL
- DLBCL associated with chronic inflammation
- ALK-positive LBCL

- EBV-positive DLBCL, NOS
- T-cell/histiocyte-rich LBCL
- LBCL with *IRF4/MUM1* rearrangement
- Fibrin-associated LBCL
- Primary mediastinal LBCL
- Mediastinal gray zone lymphoma
- High-grade B-cell lymphomas with *MYC and BCL2* rearrangements
- High-grade B-cell lymphomas, NOS
- High-grade B-cell lymphomas
- High-grade B-cell lymphomas with 11q aberrations
- LBCL with 11q aberration
- Primary cutaneous DLBCL, leg type

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose

DLBCL	Administer in 28-day cycles until disease progression or unacceptable toxicity:
	• Cycle 1:
	  ○ Day 1: step-up dose 1 – 0.16 mg SC
	  ○ Day 8: step-up dose 2 – 0.8 mg SC
	  ○ Day 15: first full dose – 48 mg SC
	  ○ Day 22: 48 mg SC
	• Cycle 2 and 3; days 1, 8, 15, 22: 48 mg SC
	• Cycles 4 to 9; days 1 and 15: 48 mg SC
	• Cycle 10 and beyond; day 1: 48 mg SC
		See regimen

FL	Administer in 28-day cycles until disease progression or unacceptable toxicity, or if administered as combination therapy, up to a total of 12 cycles, whichever occurs first:
	• Cycle 1:
	  ○ Day 1: step-up dose 1 – 0.16 mg SC
	  ○ Day 8: step-up dose 2 – 0.8 mg SC
	  ○ Day 15: step-up dose 3 – 3 mg SC
	  ○ Day 22: first full dose – 48 mg SC
	• Cycle 2 and 3; days 1, 8, 15, 22: 48 mg SC
	
	For subsequent cycles, dosing is dependent on monotherapy vs combination therapy use:
	As monotherapy:
	• Cycles 4 to 9; days 1 and 15: 48 mg SC
	• Cycle 10 and beyond; day 1: 48 mg SC
	
	In combination with lenalidomide and rituximab:
	• Cycles 4 to 12; day 1: 48 mg SC
		See regimen

VI. Product Availability

Single-dose vials for injection: 4 mg/0.8 mL, 48 mg/0.8 mL

VII. References

1. Epkinly Prescribing Information. Plainsboro, NJ: Genmab US, Inc.; March 2026. Available at: https://www.genmab-pi.com/prescribing-information/epkinly-pi.pdf. Accessed April 21, 2026.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed May 6, 2026.
3. National Comprehensive Cancer Network. B-Cell Lymphomas Version 3.2026. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed May 6, 2026.
4. National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Version 2.2026. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed May 6, 2026.
5. Thieblemont C, Phillips T, Ghesquieres H, et al. Epcoritamab, a novel, subcutaneous CD3xCD20 bispecific T-cell-engaging antibody, in relapsed or refractory large B-cell lymphoma: Dose expansion in a phase I/II trial. J Clin Oncol. 2023 Apr 20; 41(12): 2238-2247.
6. Linton KM, Vitolo U, Jurczak W, 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 Jun 13: S2352-3026(24)00166-2.
7. Linton K, Jurczak W, Lugtenburg P, et al. Epcoritamab SC monotherapy leads to deep and durable responses in patients with relapsed or refractory follicular lymphoma: First data disclosure from the Epcore NHL-1 follicular lymphoma dose-expansion cohort [abstract]. Blood 2023;142: Abstract 1655.
8. Falchi L, Nijland M, Huang H, et al. Epcoritamab, lenalidomide, and rituximab versus lenalidomide and rituximab for relapsed or refractory follicular lymphoma (EPCORE FL-1): a global, open-label, randomised, phase 3 trial. Lancet. Published online December 7, 2025. doi:10.1016/S0140-6736(25)02360-8

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J9321	Injection, epcoritamab-bysp, 0.16 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	06.01.23	08.23
Added HCPCS code [J9321]	10.27.23	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2024 annual review: added NCCN Compendium supported off-label use for classic follicular lymphoma; references reviewed and updated. RT4: updated FDA approved indications to include follicular lymphoma per updated prescribing information.	07.03.24	08.24
3Q 2025 annual review: per NCCN Compendium – added use in second-line and subsequent therapy in combination with gemcitabine and oxaliplatin; removed specific criteria requirements for histologic transformation of indolent lymphoma to DLBCL; added Appendix D to specify DLBCL subtypes per NCCN; references reviewed and updated.	04.17.25	08.25
RT4: updated with newly approved indication of combination with lenalidomide and rituximab for relapsed or refractory FL and updated accelerated approved to traditional approval for FL indications; expanded monotherapy option for B-cell lymphoma subtypes per NCCN; summarized NCCN and FDA-approved uses for improved clarity; extended initial approval duration for Medicaid/HIM from 6 months to 12 months.	12.11.25	
3Q 2026 annual review: no significant changes; clarified prior therapy requirements for DLBCL arising from CLL (Richter transformation) per NCCN Compendium; references reviewed and updated. Added ICHRA line of business.	04.21.26	08.26

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy,

contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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