Clinical Policy: Epcoritamab-bysp (Epkinly)

Reference Number: PA.CP.PHAR.634
Effective Date: 08/2023
Last Review Date: 01/2026

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 follicular lymphoma (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 trials.

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 PA Health & Wellness® that Epkinly is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

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

1. Diagnosis of one of the following (a-e):
   a. DLBCL (*see subtypes in Appendix D*);
   b. Classic Follicular Lymphoma (grades 1, 2 and 3A);
   c. Histologic transformation of indolent 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. One of the following (a, b or c):
   a. Request is for DLBCL, HIV-related B-cell lymphomas, and post-transplant lymphoproliferative disorders, except DLBCL arising from CLL (Richter transformation), and all of the following (i, ii, and iii or iv):
      i. Prescribed in combination with GemOx (gemcitabine and oxaliplatin);
      ii. Member has received ≥ 1 line of systemic therapy (*see Appendix B*);
      iii. Member has one of the following (1, 2, or 3):

1. Relapsed or refractory disease;
2. 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);
3. Relapsed disease > 12 months after completion of first-line therapy if no intention to proceed to transplant;

or

iv. Other NCCN recommendations listed as category 1, 2A, or 2B;

b. For DLBCL arising from CLL (Richter transformation), one of the folllowing (i-iii):
   i. Untreated CLL or clonally unrelated disease at initial diagnosis as additional therapy for partial response, refractory disease, or progression while on treatment with chemoimmunotherapy regimens;
   ii. Previously treated CLL* and clonally related or clonal relation unknown** as first-line treatment;
   iii. Previously treated CLL* and clonally related or clonal relation unknown** as continuation therapy for complete response until progression or as additional therapy not previously used for partial response, refractory disease, or progression while on treatment with CIT or non-CIT regimens);
   **In patients with previously treated CLL, options depend on treatment received for CLL prior to transformation*
   ***It is recommended that clonal relatedness be determined; however, if it is not feasible and CLL has not been previously treated, consider treating as clonally unrelated*
   iv. Other NCCN recommendations listed as category 1, 2A, or 2B;

c. All of the following (i, ii, and iii):
   i. Member has received ≥ 2 lines of systemic therapy (*see Appendix B*);
   ii. Member had partial response, no response, progressive, relapsed, or refractory disease following prior systemic therapy;
   iii. One of the following (1, 2 or 3):
      1. For classic FL, prescribed as one of the following (a or b):
         a. In combination with lenalidomide and rituximab for relapsed or refractory disease;*
            **Prior authorization may be required for lenalidomide and rituximab*
         b. As a single agent;
      2. All other indications: Prescribed as a single agent;
      3. Other NCCN recommendations listed as category 1, 2A, or 2B;

5. Request meets one of the following (a or b):
   a. Both 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*).

Approval duration: 12 months

B. Other diagnoses/indications

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

II. Continued Therapy

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

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies;
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*).

Approval duration: 12 months

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

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

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 – PA.CP.PMN.53

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

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 and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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
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
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		

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
<u>*Examples of first-line, second-line and subsequent therapies*</u>: • bendamustine + obinutuzumab or rituximab • CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + obinutuzumab or rituximab • CVP (cyclophosphamide, vincristine, prednisone) + obinutuzumab or rituximab • Lenalidomide + rituximab <u>*Single-agent examples*</u>: 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 large B-cell lymphoma
- 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.; June 2024. Available at: https://www.genmab-pi.com/prescribing-information/epkinly-pi.pdf. Accessed December 10, 2025.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed December 11, 2025.
3. National Comprehensive Cancer Network. B-Cell Lymphomas Version 3.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed December 11, 2025.
4. National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Version 1.2026. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed December 15, 2025.

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
Policy created	07/2023
3Q 2024 annual review: RT4: updated FDA approved indications to include follicular lymphoma per updated prescribing information; added HCPCS code [J9321]; references reviewed and updated.	07/2024
3Q 2025 annual review: RT4: updated FDA approved indications to include follicular lymphoma per updated prescribing information; 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.	07/2025
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 from 6 months to 12 months	01/2026