Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Epcoritamab-bysp (Epkinly®)	MP-RX-FP-121-24	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of *Epcoritamab-bysp (Epkinly®),* a bispecific CD20-directed CD3 T-cell engager approved by the Food and Drug Administration (FDA) 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 (HGBL), after two or more lines of systemic therapies. Epkinly is also FDA indicated in the treatment of adults with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy.

Background Information

Epcoritamab-bysp is a T-cell-engaging bispecific antibody that targets CD3/CD20, promotes T-cell activation and expansion, and cause the release of proinflammatory cytokines, eventually inducing lysis of B-cells.

The National Comprehensive Cancer Network® (NCCN) provides recommendations with a category 2A level of evidence for the use of Epkinly in these additional B-cell lymphomas: Post-transplant lymphoproliferative disorders and HIV-related B-Cell Lymphomas.

Epkinly is administered by a subcutaneous injection once every 28 days after initial step-up dosing cycles. Two dosages are available for the step-up dosing 4 mg/0.8 mL vial and a maintenance dose vial of 48 mg/0.8 mL

Epkinly has a boxed warning for serious or life-threatening cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

Definitions and Measures

- ECOG or Eastern Cooperative Oncology Group Performance Status: A scale and criteria used by doctors and researchers to assess how an individual's disease is progressing, assess how the disease affects the daily living abilities of the individual, and determine appropriate treatment and prognosis. This scale may also be referred to as the WHO (World Health Organization) or Zubrod score which is based on the following scale:
    - 0 = Fully active, able to carry on all pre-disease performance without restriction
    - 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work

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- 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- 5 = Dead

- Line of Therapy:
  - First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
  - Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
  - Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second- line therapy) are not effective or there is disease progression.
- Refractory Disease: Illness or disease that does not respond to treatment.
- Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.

Approved Indications

A. 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.
B. Treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

This indications is approved under accelerated approval based on response rate and durability of response [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Other Uses

i. Post-transplant lymphoproliferative disorders (NCCN 2A)
ii. HIV-related B-Cell Lymphomas (NCCN 2A)

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Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J9321	Injection, epcoritamab-bysp, 0.16 mg [Epkinly]

ICD-10	Description
B20	Human immunodeficiency virus [HIV] disease
C82.00-C82.99	Follicular lymphoma
C83.30-C83.39	Diffuse large B-cell lymphoma
C83.398	Diffuse large B-cell lymphoma of other extranodal and solid organ sites
C83.80-C83.89	Other non-follicular lymphoma
C85.10-C85.19	Unspecified B-cell lymphoma
C85.20-C85.29	Mediastinal (thymic) large B-cell lymphoma
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)

Medical Necessity Guidelines

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.

Epcoritamab-bysp (Epkinly®)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

i. Individual has a diagnosis of *one* of the following B-Cell Lymphomas:
   A. CD20+ relapsed or refractory diffuse large B-cell lymphoma (DLBCL), including DLBCL arising from indolent lymphoma; **OR**
   B. High-grade B-cell lymphoma (HGBL); **OR**
   C. Post-transplant lymphoproliferative disorders (NCCN 2A); **OR**
   D. HIV-related B-Cell Lymphomas (NCCN 2A); **OR**
   E. Classic Follicular lymphoma (Label, NCCN 2A); **AND**

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ii. Individual has received two or more prior lines of therapy, including at least one anti-CD20 monoclonal antibody; **AND**
iii. Individual is using in one of the following ways:
    A. Individual is using Epkinly as a single agent for any of the B-Cell Lymphomas; **OR**
    B. Individual is using Epkinly in combination with gemcitabine and oxaliplatin for DLBCL, High-Grade B-cell lymphoma, HIV-Related B-cell Lymphoma, or PTLD; **AND**
iv. Individual has an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.

B. Criteria For Continuation of Therapy

i. MMM considers continuation of Epcoritamab-bysp (Epkinly®) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) if the following information is provided:
    A. Documentation of the patient's response showing no evidence of Cytokine release syndrome (CRS) or Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS).

C. Authorization Duration

i. Initial Approval Duration: Up to 6 months
ii. Reauthorization Approval Duration: Up to 6 months

D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. Individual has central nervous system involvement of lymphoma; **OR**
ii. Individual has an ongoing active infection; **OR**
iii. Individual with known impaired T-cell immunity; **OR**
iv. When the above criteria are not met and for all other indications.

Limits or Restrictions

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

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Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Epcoritamab-bysp (Epkinly®)

Cycle of treatment (Cycle=28 days)	Day of treatment	Dose of Epkinly (epcoritamab-bysp) Injection: 4 mg/0.8 mL SDV, 48 mg/0.8 mL SDV	
DLBCL and High-grade B-cell Lymphoma			
Cycle 1	1	Step-up dose 1	0.16 mg
	8	Step-up dose 2	0.8 mg
	15	First full dose	48 mg
	22	48 mg	
Cycles 2 and 3	1, 8, 15 and 22	48 mg	
Cycles 4 to 9	1 and 15	48 mg	
Cycles 10 and beyond	1	48 mg	
Follicular Lymphoma			
Cycle 1	1	Step-up dose 1	0.16 mg
	8	Step-up dose 2	0.8 mg
	15	Step-up dose 3	3 mg
	22	First full dose	48 mg

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Cycles 2 and 3	1, 8, 15 and 22	48 mg
Cycles 4 to 9	1 and 15	48 mg
Cycles 10 and beyond	1	48 mg

Exceptions

- All patients should be monitored for
  - Signs and symptoms of CRS and ICANS.
  - Signs or symptoms of infections.
  - Complete blood cell counts during treatment.
- Patients with DLBCL or high-grade B-cell lymphoma should be hospitalized for 24 hours after administration of the Cycle 1 Day 15 dosage of 48 mg to prevent the risk of CRS and ICANS.
- Prophylaxis for Pneumocystis jirovecii pneumonia (PJP) and Herpes virus are recommended prior to starting treatment with Epkinly.

Reference Information

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: June 2, 2023.
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.

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.

Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Annual Revision 11/17/2025	Clarify NCCN nomenclature for follicular lymphoma (FL) to classic FL. Add NCCN recommendation for combination use with Gem/Ox and Epkinly in DLBCL, High-Grade, HIV-related, and PTLD B-cell lymphomas. Coding Reviewed: Removed ICD-10-CM	12/3/2025	12/11/2025

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	C83.39. Added ICD-10-CM B20, C83.398, C83.80-C83.89, C85.10-C85.19, C85.20-C85.29, D47.Z1.		
Annual Review 12/20/2024	Updated service description, approved indications, and other uses to include new FDA label indication and 2A NCNN recommendations for the use of Epkinly. Updated criteria for initial approval: added 2A recommendations for additional B-cell lymphomas and new FDA approval for use in relapsed/refractory follicular lymphoma. Updated quantity limits table to add dosage form and strenghts, dose for new indications and update exceptions per FDA label. Minor wording and formatting changes. Coding Reviewed: Add ICD-10-CM C82.00-C82.99.	3/20/2025	4/2/2025
Policy Inception 01/26/2024	New Medical Policy creation	4/18/2024	6/28/2024