09-J4000-61

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Subject: Epcoritamab-bysp (Epkinly) SQ Injection

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DESCRIPTION:

Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma (NHL) and accounts for approximately one-third of NHL patients. The highest incidence of DLBCL is among patients equal to or older than 65 years of age; however, it can present in pediatric patients. The clinical presentation typically consists of swollen or enlarged lymph nodes, unexplained weight loss (greater than 10% body weight in prior 6 months), night sweats, and fever (greater than 100.4 degrees F for greater than or equal to 3 days).

DLBCL are generally aggressive, but potentially curable in the majority of patients. Initial treatment for DLBCL includes combination chemotherapy plus rituximab such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) or Pola-R-CHP (polatuzumab vedotin-piiq, rituximab, cyclophosphamide, doxorubicin, and prednisone). This can lead to survival rates of approximately 70%, 60%, and 45% at 3, 5, and 10 years, respectively, after diagnosis. Unfortunately, about 30 to 40 percent of patients with DLBCL relapse. Therefore, second line therapies may include bendamustine with rituximab, brentuximab vedotin (Adcetris) for CD30+ tumors, CEPP (cyclophosphamide, etoposide, prednisone, procarbazine, rituximab), CEOP (cyclophosphamide, etoposide, vincristine, prednisone, rituximab), GDP (gemcitabine, dexamethasone, carboplatin, with rituximab), lenalidomide (Revlimid) with rituximab, and ibrutinib (Imbruvica). If relapse occurs in less than 12 months or for primary refractory disease, anti-CD19 chimeric antigen receptor (CAR) T-cell therapy may be considered.

On May 19, 2023, the FDA granted accelerated approval to epcoritamab-bysp (Epkinly) 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, and in June 2024, the FDA granted approval as monotherapy for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. In November 2025, the FDA approved epcoritamab-bysp (Epkinly) for use in combination with lenalidomide and rituximab for the treatment of adult patients with relapsed or refractory follicular lymphoma. Epcoritamab-bysp (Epkinly) is a T-cell engaging

bispecific antibody that binds to the CD3 receptor expressed on the surface of T-cells and CD20 expressed on the surface of lymphoma cells and healthy B-lineage cells. Epcoritamab-activated T-cells cause the release of proinflammatory cytokines and induce lysis of B-cells.

The efficacy and safety of epcoritamab-bysp (Epkinly) was evaluated in the dose expansion cohort of a Phase 1-to-2, open-label, multicenter, single-arm trial. Eligible patients included those 18 years of age and older with an Eastern Cooperative Oncology Group performance status of 0 to 2 (on a 5-point scale, with higher numbers indicating greater disability) and documented $CD20^+$ mature B-cell neoplasm (diffuse large B-cell lymphoma [DLBCL] or other aggressive non-Hodgkin lymphoma, including primary mediastinal LBCL, high-grade B-cell lymphoma, or follicular lymphoma grade 3B). Other inclusion criteria were relapsed or refractory disease and treatment with at least two prior lines of systemic therapy, including at least one anti-CD20–containing regimen. A total of 157 patients were enrolled and received epcoritamab-bysp (Epkinly) monotherapy as a subcutaneous injection according to the following 28-day cycle schedule:

- Cycle 1: 0.16 mg on Day 1, 0.8 mg on Day 8, 48 mg on Days 15 and 22
- Cycles 2-3: 48 mg on Days 1, 8, 15, and 22
- Cycles 4-9: 48 mg on Days 1 and 15
- Cycles 10 and beyond: 48 mg on Day 1

Premedication (e.g., corticosteroid, antihistamine, acetaminophen) for cytokine release syndrome (CRS) was administered during Cycle 1 in all patients and 24-hour inpatient monitoring was required for the first full dose. Patients continued to receive epcoritamab-bysp (Epkinly) until disease progression or unacceptable toxicity. The primary end point was overall response rate (ORR) by an independent review committee. Secondary end points included duration of response (DOR), complete response (CR) rate, duration of CR, progression-free survival (PFS), time to response, and overall survival. Epcoritamab-bysp (Epkinly) provided an ORR of 63.1% with a CR of 38.9%. The median DOR was 12 months (95% confidence interval [CI], 6.6 months to not reached) with a median of 1.4 months to response. Median PFS was 4.4 months (95% confidence interval [CI], 3 to 7.9 months), and the PFS-rate at 6 months was 43.9%. Median overall survival was not reached (95% confidence interval [CI], 11.3 months to not reached). Discontinuation of epcoritamab-bysp (Epkinly) due to adverse events (any Grade) occurred in 7.6% of the patients. Treatment-related adverse events, Grade 3 or higher occurred in 26.8% of patients and included CRS (49.7%), injection site reaction (19.7%), and neutropenia (17.8%). No Grade 4 or 5 CRS events were observed. Immune effector cell-associated neurologic toxicity syndrome (ICANS) occurred in 6.4% of patients and clinical tumor lysis syndrome occurred in 1.3%.

The efficacy of epcoritamab-bysp (Epkinly) as monotherapy for follicular lymphoma (FL) was evaluated in EPCORE NHL-1, an open-label, multi-cohort, multicenter, single-arm trial that included patients with relapsed or refractory disease after at least 2 lines of systemic therapy. The study excluded patients with CNS involvement of lymphoma, allogeneic HSCT or solid organ transplant, ongoing active infection, any patients with known impaired T-cell immunity, creatinine clearance < 45 mL/min, alanine aminotransferase > 3 times the upper limit of normal, and a cardiac ejection fraction < 45%. Patients received epcoritamab-bysp (Epkinly) monotherapy following a 2-step up dosage schedule:

- Cycle 1: 0.16 mg on Day 1, 0.8 mg on Day 8, 48 mg on Days 15 and 22
- Cycles 2-3: 48 mg on Days 1, 8, 15, and 22

- Cycles 4-9: 48 mg on Days 1 and 15
- Cycles 10 and beyond: 48 mg on Day 1

Patients continued to receive epcoritamab-bysp (Epkinly) until disease progression or unacceptable toxicity. Among the 127 patients with FL, the median age was 65 years (range: 39 to 84), 52% were 65 years of age or older, and 62% were male. Race was reported in 85 (67%) patients; of these patients, 89% were Caucasian and 8% were Asian. A total of 85% had stage III-IV disease, 25% had bulky disease, 95% had an ECOG performance status of 0 or 1, and 6% had an ECOG performance status of 2. The median number of prior therapies was 3 (range: 2 to 9), with 36% receiving 2 prior lines of systemic therapy, 32% receiving 3 prior therapies, and 32% receiving 4 or more prior therapies. Seventy-nine percent of patients were refractory to prior anti-CD20 monoclonal antibody therapy, 70% were refractory to both anti-CD20 monoclonal antibody and alkylator therapy, 21% had prior rituximab plus lenalidomide therapy, 19% received prior autologous HSCT, and 5% received prior chimeric antigen receptor (CAR) T-cell therapy. Fifty-two percent of patients had progression of disease within 24 months of first systemic therapy. Efficacy of epcoritamab-bysp (Epkinly) monotherapy for FL was as follows: overall response rate (ORR) of 104 (82%), complete response of 76 (60%), and partial response of 28 (22%). The median duration of response was not reached with an estimated 12-month duration of response of 68.4% using Kaplan-Meier estimate.

The efficacy of epcoritamab-bysp (Epkinly) in combination with lenalidomide and rituximab for FL was evaluated in EPCORE FL-1, an open-label, randomized, multicenter, global trial in patients with relapsed or refractory disease after at least one line of systemic therapy. Patients were randomized to receive epcoritamab-bysp (Epkinly) in combination with lenalidomide and rituximab or lenalidomide and rituximab alone. The study excluded patients with known CNS involvement by lymphoma, prior allograft, and known active infection. Patients received epcoritamab-bysp (Epkinly) via subcutaneous injection in 28-day cycles for a total of 12 cycles or until disease progression or unacceptable toxicity, whichever occurred first. The recommended epcoritamab-bysp (Epkinly) dosage schedule was:

- Cycle 1: 0.16 mg on Day 1, 0.8 mg on Day 8, 3 mg on Day 15 and 48 mg on Day 22
- Cycles 2-3: 48 mg on Days 1, 8, 15, and 22
- Cycles 4-12: 48 mg on Day 1

In both treatment arms, lenalidomide was given orally at a dose of 20 mg once daily from Days 1 to 21 for 12 cycles and rituximab was administered intravenously at a dose of 375 mg/m^2 on Days 1, 8, 15, and 22 of Cycle 1, followed by administration on Day 1 of Cycles 2 to 5. Of all patients randomized, the median age was 61 years (range: 24 to 89 years), with 40% being age 65 or older; 57% were male; 72% were Caucasian, 24% Asian, and 2% were African American; and 98% had an ECOG performance status of 0 or 1. The median number of prior lines of systemic therapy was 1 (range: 1 to 7) with 24% receiving 2 prior lines and 17% receiving 3 or more prior lines of therapy. Forty-one percent had progressive disease within 24 months of first systemic therapy. Efficacy results of lenalidomide and rituximab with and without epcoritamab-bysp (Epkinly) are provided in Table 1 and are based on a median duration of follow-up of 10.4 months in the intention-to-treat population.

Table 1: Efficacy results of lenalidomide and rituximab with and without epcoritamab-bysp (Epkinly) for FL

Outcome	Lenalidomide and Rituximab with Epcoritamab-bysp (N=243)	Lenalidomide and Rituximab (N=245)
Progression free survival (PFS)		
Number of events, n (%)	23 (9)	75 (31)
Progressive disease	19 (83)	63 (84)
Death	4 (17)	12 (16)
Median (95% CI), months	NR (21.9, NR)	11.2 (10.5, NR)
Hazard ratio[a] (95% CI)	0.21 (0.13, 0.33)	
P-value[b]	< 0.0001	
Overall response rate (ORR), n (%)	216 (89)	181 (74)
(95% CI)	(84, 93)	(68, 79)
P-value[c,d]	< 0.0001	
Complete response (CR), n (%)	181 (74)	106 (43)
(95% CI)	(69, 80)	(37, 50)
P-value[d]	< 0.0001	

NR = not reached

[a]Cox proportional hazards hazard ratio stratified by disease history and region.

[b]Log-rank p-value (one sided) stratified by disease history and region.

[c]P-value is based on a prespecified analysis of the first 232 patients randomized.

[d]P-value (one sided) is from a Cochran-Mantel-Haenszel test stratified by disease history and region.

After a median duration of follow-up of 14.8 months overall, the median overall survival had not been reached in either arm with a total of 35 deaths: 10 (4%) deaths in the lenalidomide and rituximab with epcoritamab-bysp (Epkinly) arm and 25 (10%) deaths in the lenalidomide and rituximab arm.

The NCCN compendia also lists epcoritamab-bysp (Epkinly) as a third-line option for HIV-related B-cell lymphoma (e.g., diffuse large B-cell lymphoma, primary effusion lymphoma, HHV8-positive DLBCL, not otherwise specified), diffuse large B-cell lymphoma, including DLBCL transformed from indolent lymphoma, high-grade B-cell lymphoma, including high-grade B-cell lymphoma, NOS and high-grade B-cell lymphomas with translocation of *MYC* and *BCL2* and/or *BCL6* (double-/triple-hit lymphoma), and monomorphic post-transplant lymphoproliferative disorder (PTLD) (B-cell type). Additionally, epcoritamab-bysp (Epkinly) is a non-chemoimmunotherapy option in NCCN for DLBCL arising from chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) [a.k.a., Richter transformation].

POSITION STATEMENT:

Administration of epcoritamab-bysp (Epkinly) **meets the definition of medical necessity** when **ANY** of the following are met ("1" or "2"):

1. **ALL** of the following ("a" to "c"):
    a. Member has a confirmed diagnosis of **ANY** of the following ("i" to "vi") - *medical record documentation confirming the patient's diagnosis and complete treatment history must be submitted*:
        i. HIV-related B-cell lymphoma that includes any of the following subtypes:
            - Diffuse large B-cell lymphoma (DLBCL)
            - Primary effusion lymphoma
            - HHV8-positive DLBCL, not otherwise specified (NOS)
        ii. Diffuse large B-cell lymphoma (DLBCL) [including DLBCL transformed from indolent lymphoma]
        iii. High-grade B-cell lymphoma [includes high-grade B-cell lymphoma, NOS and high-grade B-cell lymphomas with translocation of *MYC* and *BCL2* and/or *BCL6* (double-/triple-hit lymphoma)]
        iv. Monomorphic post-transplant lymphoproliferative disorder (PTLD) (B-cell type)
        v. Follicular lymphoma (FL)
        vi. DLBCL arising from CLL/SLL [a.k.a., Richter transformation]
    b. One of the following:
        i. Used as either third-line or subsequent therapy as a single agent therapy
        ii. Used as either second-line or subsequent therapy in combination with gemcitabine and oxaliplatin for any of the following:
            a. HIV-related B-cell lymphoma [including Diffuse large B-cell lymphoma (DLBCL), primary effusion lymphoma, HHV8-positive DLBCL, not otherwise specified (NOS)]
            b. Diffuse large B-cell lymphoma (DLBCL)
            c. High-grade B-cell lymphoma
            d. Monomorphic post-transplant lymphoproliferative disorder (PTLD) (B-cell type)
        iii. Used as either second-line or subsequent therapy in combination with lenalidomide and rituximab for relapsed or refractory follicular lymphoma (FL)
        iv. Used as non-chemoimmunotherapy for DLBCL arising from CLL/SLL [a.k.a., Richter transformation]
    c. Dosage of epcoritamab-bysp (Epkinly) does not exceed the following:
        i. Cycle 1 ("a" or "b"):

a. B-cell lymphomas: 0.16 mg SC on Day 1 (Step-up dose 1), 0.8 mg SC on Day 8 (Step-up dose 2), 48 mg SC on Days 15 (First treatment dose) and 22

b. Follicular lymphoma: 0.16 mg SC on Day 1 (Step-up dose 1), 0.8 mg SC on Day 8 (Step-up dose 2), 3 mg SC on Day 15 (Step-up dose 3), and 48 mg SC on Day 22 (First treatment dose)

ii. Cycles 2-3: 48 mg SC on Days 1, 8, 15, and 22

iii. Cycles 4-9: 48 mg SC on Days 1 and 15 or 48 mg SC on Day 1 when used in combination with lenalidomide and rituximab

iv. Cycles 10 and beyond: 48 mg SC on Day 1

2. Member has another FDA-approved or NCCN-supported diagnosis, and **ALL** of the following criteria are met ("a", "b", and "c"):

   a. **EITHER** of the following ("i" or "ii"):

      i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert), **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)

      ii. Indication **AND** usage are recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

   b. Epcoritamab-bysp (Epkinly) is used in a treatment regimen in accordance with the FDA-approved prescribing information or applicable NCCN guideline recommendation for the diagnosis

   c. Dosage of epcoritamab-bysp (Epkinly) does not exceed the maximum recommended in the FDA-approved prescribing information or the maximum recommended by the applicable NCCN guidelines for the diagnosis

Approval duration: 1 year

Continuation* of epcoritamab-bysp (Epkinly) meets the definition of medical necessity when **ALL** of the following criteria are met ("1" to "2"):

1. An authorization or reauthorization for epcoritamab-bysp (Epkinly) has been previously approved by Florida Blue or another health plan in the past 2 years (if another health plan, documentation of a health plan-paid claim during the 90 days before the authorization request must be submitted) for diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, high-grade B-cell lymphoma, follicular lymphoma, and DLBCL arising from CLL/SLL [a.k.a., Richter transformation], or other FDA-approved or NCCN-supported diagnosis; **OR** the member previously met **ALL** indication-specific initiation criteria

2. **EITHER** of the following based on the member's diagnosis ("a" or "b"):

   a. For HIV-related B-cell lymphoma [including Diffuse large B-cell lymphoma (DLBCL), primary effusion lymphoma, HHV8-positive DLBCL, not otherwise specified (NOS)], diffuse large B-cell lymphoma (DLBCL) [including DLBCL transformed from indolent lymphoma], High-grade B-cell lymphoma [includes high-grade B-cell lymphoma, NOS and high-grade B-cell lymphomas with translocation of *MYC* and *BCL2* and/or *BCL6* (double-/triple-hit lymphoma)], Monomorphic post-

transplant lymphoproliferative disorder (PTLD) (B-cell type), follicular lymphoma, and DLBCL arising from CLL/SLL [a.k.a., Richter transformation], and **ALL** of the following ("i", "ii", and "iii"):

i. Epcoritamab-bysp (Epkinly) will be used in combination with gemcitabine and oxaliplatin for HIV-related B-cell lymphoma [including Diffuse large B-cell lymphoma (DLBCL), primary effusion lymphoma, HHV8-positive DLBCL, not otherwise specified (NOS)], diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma, or monomorphic post-transplant lymphoproliferative disorders (PTLD), in combination with lenalidomide and rituximab for FL, or as a single-agent therapy

ii. Provider attestation that the member has not had disease progression during epcoritamab-bysp (Epkinly) treatment

iii. Dosage of epcoritamab-bysp (Epkinly) does not exceed the following:

- Cycle 1 ("a" or "b"):
    a. B-cell lymphomas: 0.16 mg SC on Day 1 (Step-up dose 1), 0.8 mg SC on Day 8 (Step-up dose 2), 48 mg SC on Days 15 (First treatment dose) and 22
    b. Follicular lymphoma: 0.16 mg SC on Day 1 (Step-up dose 1), 0.8 mg SC on Day 8 (Step-up dose 2), 3 mg SC on Day 15 (Step-up dose 3), and 48 mg SC on Day 22 (First treatment dose)
- Cycles 2-3: 48 mg SC on Days 1, 8, 15, and 22
- Cycles 4-9: 48 mg SC on Days 1 and 15 or 48 mg SC on Day 1 when used in combination with lenalidomide and rituximab
- Cycles 10 and beyond: 48 mg SC on Day 1

b. Other FDA-approved or NCCN-supported diagnosis, and **ALL** of the following ("i", "ii", and "iii"):

i. Dosage of epcoritamab-bysp (Epkinly) does not exceed the maximum recommended in the FDA-approved prescribing information or the maximum recommended by the applicable NCCN guideline for the specific diagnosis

ii. Epcoritamab-bysp (Epkinly) is used in a treatment regimen in accordance with the FDA-approved prescribing information or applicable NCCN guideline recommendation for the diagnosis

iii. Member has had a beneficial response to treatment with epcoritamab-bysp (Epkinly)

Approval duration: 1 year

** For members that may have only completed the initial step-up dosing schedule during an inpatient admission, please refer to the initiation criteria*

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Epcoritamab-bysp (Epkinly) is a bispecific CD20-directed CD3 T-cell engager 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, high-grade B-cell lymphoma, and relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. Epcoritamab-bysp (Epkinly) is also indicated for use in combination with lenalidomide and rituximab for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL).
- Epcoritamab (Epkinly) is administered subcutaneously according to the following 28-day cycle schedules:
- Schedule for DLBCL and high-grade B-cell lymphoma and monotherapy for FL
    - Cycle 1:
        - B-cell lymphomas: 0.16 mg on Day 1 (Step-up dose 1), 0.8 mg on Day 8 (Step-up dose 2), 48 mg on Days 15 (First treatment dose) and 22
        - Follicular lymphoma: 0.16 mg SC on Day 1 (Step-up dose 1), 0.8 mg SC on Day 8 (Step-up dose 2), 3 mg SC on Day 15 (Step-up dose 3), and 48 mg SC on Day 22 (First treatment dose)
    - Cycles 2-3: 48 mg on Days 1, 8, 15, and 22
    - Cycles 4-9: 48 mg on Days 1 and 15
    - Cycles 10 and beyond: 48 mg on Day 1
- Schedule for FL in combination with lenalidomide and rituximab
    - Cycle 1: 0.16 mg SC on Day 1 (Step-up dose 1), 0.8 mg SC on Day 8 (Step-up dose 2), 3 mg SC on Day 15 (Step-up dose 3), and 48 mg SC on Day 22 (First treatment dose)
    - Cycles 2-3: 48 mg on Days 1, 8, 15, and 22
    - Cycles 4-12: 48 mg on Day 1
- Epcoritamab (Epkinly) is prepared and administered by a healthcare professional. The 0.16 mg and 0.8 mg doses require dilution prior to administration.
- It is recommended to inject the product into the subcutaneous tissue of the lower part of the abdomen (preferred injection site) or the thigh. Change of injection site from the left or right side or vice versa is recommended, especially during the weekly administrations (Cycles 1 to 3). Do not inject into tattoos or scars or areas where the skin is red, bruised, tender, hard, or not intact.
- Premedication with a corticosteroid (e.g., prednisolone 100 mg oral or intravenous, dexamethasone 15 mg oral or intravenous), an antihistamine such as diphenhydramine 50 mg orally or intravenous, and acetaminophen 650 to 1,000 mg orally is recommended to prevent and/or minimize the Cytokine Release Syndrome (CRS).
- Administration of epcoritamab (Epkinly) should occur in a facility equipped to monitor and manage CRS. 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. For patients with FL, assess whether hospitalization or outpatient monitoring is appropriate after administration of the Cycle 1 Day 22 dosage of 48 mg.
- Prior to starting epcoritamab (Epkinly), consider initiation of antiviral prophylaxis to prevent herpes virus reactivation and PJP prophylaxis in patients at increased risk

Dose Adjustments

- The effect of renal or hepatic impairment on the pharmacokinetics of epcoritamab-bysp (Epkinly) is unknown.
- Recommendations for restarting epcoritamab (Epkinly) after dose delays for DLBCL or High-grade B-cell Lymphoma are as follows:

Last Dose Administered	Time Since the Last Dose Administered	Action for Next Dose(s)[a]
0.16 mg on Cycle 1 Day 1	More than 8 days	Repeat Cycle 1 schedule starting at step-up dose 1 (0.16 mg). Following the repeat of Cycle 1 schedule, resume the planned treatment schedule.
0.8 mg on Cycle 1 Day 8	14 days or less	Administer 48 mg , then resume the planned treatment schedule
	More than 14 days	Repeat Cycle 1 schedule starting at step-up dose 1 (0.16 mg). Following the repeat of Cycle 1 schedule, resume the planned treatment schedule.
48 mg on Cycle 1 Day 15 onwards	6 weeks or less	Administer 48 mg, then resume the planned treatment schedule.
	More than 6 weeks	Repeat Cycle 1 schedule starting at step-up dose 1 (0.16 mg). Following the repeat of Cycle 1 schedule, resume the planned treatment schedule.

[a] Administer pretreatment medication prior to epcoritamab-bysp (Epkinly) dose and monitor patients accordingly.

- Recommendations for restarting epcoritamab (Epkinly) after dose delays for FL are as follows:

Last Dose Administered	Time Since the Last Dose Administered	Action for Next Dose(s)[a]
0.16 mg on Cycle 1 Day 1	More than 8 days	Repeat Cycle 1 schedule starting at step-up dose 1 (0.16 mg). Following the repeat of Cycle 1 schedule, resume the planned treatment schedule.

0.8 mg on Cycle 1 Day 8	More than 8 days	Repeat Cycle 1 schedule starting at step-up dose 1 (0.16 mg). Following the repeat of Cycle 1 schedule, resume the planned treatment schedule.
3 mg on Cycle 1 Day 15	14 days or less	Administer 48 mg, then resume the planned treatment schedule.
	More than 14 days	Repeat Cycle 1 schedule starting at step-up dose 1 (0.16 mg). Following the repeat of Cycle 1 schedule, resume the planned treatment schedule
48 mg on Cycle 1 Day 22 onwards	6 weeks or less	Administer 48 mg, then resume the planned treatment schedule.
	More than 6 weeks	Repeat Cycle 1 schedule starting at step-up dose 1 (0.16 mg). Following the repeat of Cycle 1 schedule, resume the planned treatment schedule.

[a] Administer pretreatment medication prior to epcoritamab-bysp (Epkinly) dose and monitor patients accordingly

Drug Availability

- Epcoritamab-bysp (Epkinly) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution, free of visible particles, supplied in glass vials as follows:
  - One 4 mg/0.8 mL single-dose vial (NDC 82705-002-01)
  - One 48 mg/0.8 mL single-dose vial (NDC 82705-010-01)

PRECAUTIONS:

Boxed Warning

- Cytokine release syndrome (CRS), including serious or life-threatening reactions, can occur in patients receiving epcoritamab-bysp (Epkinly). Initiate treatment with the epcoritamab-bysp (Epkinly) step-up dosing schedule to reduce the incidence and severity of CRS. Withhold therapy 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-bysp (Epkinly). Monitor patients for neurological signs or symptoms of ICANS during treatment. Withhold therapy until ICANS resolves or permanently discontinue based on severity.

Contraindications

- None

Precautions/Warnings

- **Infections:** Epcoritamab-bysp (Epkinly) can cause serious or fatal infections. Monitor patients for signs or symptoms of infection, including opportunistic infections, and treat appropriately.
- **Cytopenias:** Monitor complete blood cell counts during epcoritamab-bysp (Epkinly) treatment.
- **Embryo-Fetal Toxicity:** Epcoritamab-bysp (Epkinly) may cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J9321	Injection, epcoritamab-bysp, 0.16 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

B20	Human immunodeficiency virus [HIV] disease [for AIDS-related B-cell lymphomas only and only used in combination with C83.30-C83.39, C83.80-C83.89, or C85.80-C85.89]
C82.00 – C82.09	Follicular lymphoma grade I
C82.10 – C82.19	Follicular lymphoma grade II
C82.20 – C82.29	Follicular lymphoma grade III
C82.30 – C82.39	Follicular lymphoma grade IIIa
C82.40 – C82.49	Follicular lymphoma grade IIIb
C82.50 – C82.59	Diffuse follicle center lymphoma
C82.60 – C82.69	Cutaneous follicle center lymphoma
C82.80 – C82.89	Other types of follicular lymphoma
C82.90 – C82.99	Follicular lymphoma, unspecified
C83.00 – C83.09	Small cell B-cell lymphoma
C83.30 – C83.38	Diffuse large B-cell lymphoma
C83.390	Primary central nervous system lymphoma
C83.398	Diffuse large B-cell lymphoma of other extranodal and solid organ sites
C83.80 – C83.89	Other non-follicular lymphoma
C83.90 – C83.99	Non-follicular (diffuse) lymphoma, unspecified
C85.10 – C85.19	Unspecified B-cell lymphoma
C85.80 – C85.89	Other specified types of non-Hodgkin lymphoma

C91.10 - C91.12	Chronic lymphocytic leukemia
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 12/10/25.

GUIDELINE UPDATE INFORMATION:

09/15/23	New Medical Coverage Guideline – Epcoritamab-bysp as a third-line or subsequent monotherapy for HIV-related B-cell lymphoma, diffuse large B-cell lymphoma, high-grade B-cell lymphoma, and monomorphic post-transplant lymphoproliferative disorder.
10/01/23	Revision: Added HCPCS code C9155.
11/15/23	Revision to guideline consisting of updating the position statement to change the initial approval duration from 6 months to 1 year.
01/01/24	Revision: Added HCPCS code J9321 and deleted codes C9155 and J9999.
09/15/24	Review and revision to guideline consisting of revising the position statement and dosing/administration section to include the new FDA approved indication for relapsed or refractory follicular lymphoma and its associated dosing, adding billing codes, and updating references.
10/01/24	Revision: Updating ICD-10 billing codes.
09/15/25	Review and revision to guideline consisting of revising the position statemen to include the NCCN 2A recommendations of combination therapy with gemcitabine and oxaliplatin as second-line or subsequent therapy for HIV-related B-cell lymphomas, diffuse large B-cell lymphoma, high-grade B-cell lymphoma, or monomorphic post-transplant lymphoproliferative disorder (B-cell type).
01/15/26	Revision to guideline consisting of revising the position statement to include the new FDA approved indication of combination therapy with lenalidomide and rituximab for the treatment of relapsed or refractory follicular lymphoma and the NCCN recommendation as non-chemoimmunotherapy for DLBCL arising from CLL/SLL [a.k.a., Richter transformation] and updating the dosage section, coding, and references.