HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EPKINLY safely and effectively. See full prescribing information for EPKINLY.

EPKINLY® (epcoritamab-bysp) injection, for subcutaneous use
Initial U.S. Approval: 2023

WARNING: CYTOKINE RELEASE SYNDROME and IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

See full prescribing information for complete boxed warning.

Cytokine release syndrome (CRS), including serious or fatal reactions, can occur in patients receiving EPKINLY. Initiate treatment with the EPKINLY step-up dosage schedule to reduce the incidence and severity of CRS. Withhold EPKINLY until CRS resolves or permanently discontinue based on severity. (2.1, 2.2, 2.6, 5.1)

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), including life-threatening and fatal reactions, can occur with EPKINLY. Monitor patients for neurological signs or symptoms of ICANS during treatment. Withhold EPKINLY until ICANS resolves or permanently discontinue based on severity. (2.1, 2.2, 2.6, 5.2)

---------- RECENT MAJOR CHANGES ----------

Indications and Usage (1.2)	11/2025
Dosage and Administration (2.1)	3/2026
Dosage and Administration (2.2, 2.5, 2.6)	11/2025
Warnings and Precautions (5.1)	3/2026
Warnings and Precautions (5.2, 5.4)	11/2025
Warnings and Precautions, Infections (5.3)	6/2026

---------- INDICATIONS AND USAGE ----------

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, and high-grade B-cell lymphoma after two or more lines of systemic therapy. (1.1)
  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).
- In combination with lenalidomide and rituximab for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL). (1.2)
- As monotherapy for the treatment of adult patients with relapsed or refractory FL after two or more lines of systemic therapy. (1.2)

---------- DOSAGE AND ADMINISTRATION ----------

- For subcutaneous injection only. (2.2)
- Recommended Dosage: (2.2)

DLBCL and High-grade B-cell Lymphoma

Cycle[a]	Day	Dose of EPKINLY	
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	
Cycle 10 and beyond	1	48 mg	

[a] Cycle = 28 days

EPKINLY as Monotherapy for FL

Cycle[a]	Day	Dose of EPKINLY	
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
Cycles 2 and 3	1, 8, 15 and 22	48 mg	
Cycles 4 to 9	1 and 15	48 mg	
Cycle 10 and beyond	1	48 mg	

[a] Cycle = 28 days

EPKINLY in Combination with Lenalidomide and Rituximab for FL

Cycle[a]	Day	Dose of EPKINLY	
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
Cycles 2 and 3	1, 8, 15, and 22	48 mg	
Cycles 4 to 12	1	48 mg	

[a] Cycle = 28 days

- Monitor all patients for signs and symptoms of CRS and ICANS. (2.1)
- For patients with DLBCL or high-grade B-cell lymphoma, assess whether hospitalization or outpatient monitoring is appropriate after administration of the Cycle 1 Day 15 dosage of 48 mg. (2.1)
- For patients with FL, assess whether hospitalization or outpatient monitoring is appropriate after administration of the Cycle 1 Day 22 dosage of 48 mg. (2.1)
- Administer premedications, post-medications, and prophylaxis as recommended. (2.4, 2.5)
- Dosages of EPKINLY 0.16 mg and 0.8 mg require dilution prior to administration. (2.7, 2.8)
- See Full Prescribing Information for instructions on preparation and administration. (2.7, 2.8, 2.9, 2.10)

---------- DOSAGE FORMS AND STRENGTHS ----------

- Injection: 4 mg/0.8 mL in a single-dose vial. (3)
- Injection: 48 mg/0.8 mL in a single-dose vial. (3)

---------- CONTRAINDICATIONS ----------

None. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Infections: Can cause fatal or serious infections. Monitor patients for signs or symptoms of infection, including opportunistic infections, and treat appropriately. (5.3)
- Cytopenias: Monitor complete blood cell counts during treatment. (5.4)
- Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception. (5.5, 8.1, 8.3)

---------- ADVERSE REACTIONS ----------

EPKINLY as monotherapy for LBCL or FL: The most common (≥ 20%) adverse reactions are CRS, injection site reactions, fatigue, musculoskeletal pain, fever, diarrhea, COVID-19, rash and abdominal pain. The most common Grade 3 to 4 laboratory abnormalities (≥ 10%) are decreases in lymphocyte count, neutrophil count, hemoglobin, and platelets. (6.1)

EPKINLY in combination with lenalidomide and rituximab for FL: The most common (≥ 20%) adverse reactions are rash, upper respiratory tract infections, fatigue, injection site reactions, constipation, diarrhea, CRS, pneumonia, COVID-19, and fever. The most common Grade 3 to 4 laboratory abnormalities (≥ 10%) are decreased neutrophil count, lymphocyte count, and platelets. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genmab US, Inc. at 1-855-4GENMAB (1-855-443-6622) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME AND IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

Cytokine release syndrome (CRS), including serious or fatal reactions, can occur in patients receiving EPKINLY. Initiate treatment with the EPKINLY step-up dosage schedule to reduce the incidence and severity of CRS. Withhold EPKINLY until CRS resolves or permanently discontinue based on severity *[see Dosage and Administration (2.1, 2.2, 2.6) and Warnings and Precautions (5.1)]*.

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), including life-threatening and fatal reactions, can occur with EPKINLY. Monitor patients for neurological signs or symptoms of ICANS during treatment. Withhold EPKINLY until ICANS resolves or permanently discontinue based on severity *[see Dosage and Administration (2.1, 2.2, 2.6) and Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

1.1 DLBCL and High-grade B-cell Lymphoma

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.

This indication is approved under accelerated approval based on response rate and durability of response *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

1.2 Follicular Lymphoma

EPKINLY is indicated in combination with lenalidomide and rituximab for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL).

EPKINLY is indicated as monotherapy for the treatment of adult patients with relapsed or refractory FL after two or more lines of systemic therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Information

- Certain doses of EPKINLY require **dilution** prior to administration. There are 2 available methods to prepare **diluted** EPKINLY:

    - Empty sterile vial method as described in subsection 2.7 *[see Dosage and Administration (2.7)]*, or
    - Sterile syringe method as described in subsection 2.8 *[see Dosage and Administration (2.8)]*.

- Preparation of 3 mg and 48 mg EPKINLY doses does not require dilution. *[see Dosage and Administration (2.9)]*.

- EPKINLY should only be administered by a qualified healthcare professional with appropriate medical support to manage severe reactions such as CRS and ICANS *[see Warnings and Precautions (5.1, 5.2)]*.

- Administer EPKINLY to well-hydrated patients.

- Premedicate before each dose in Cycle 1 *[see Dosage and Administration (2.4)]*.

- Administer EPKINLY subcutaneously according to the recommended step-up dosage schedule to reduce the incidence and severity of CRS *[see Dosage and Administration (2.2)]*.

- Due to the risk of CRS and ICANS, monitor all patients for signs and symptoms *[see Dosage and Administration (2.6)]*. Assess whether hospitalization or outpatient monitoring is appropriate based on comorbidities or other situational factors for the first 48 mg dosage of EPKINLY for patients with:
    - DLBCL or high-grade B-cell lymphoma: on Cycle 1 Day 15 *[see Dosage and Administration (2.2)]*.
    - FL: on Cycle 1 Day 22 *[see Dosage and Administration (2.2)*].

2.2 Recommended Dosage

EPKINLY is for subcutaneous injection only.

The recommended DLBCL dosage for Cycle 1 consists of 2 step-up doses, and the recommended FL dosage (monotherapy or in combination with lenalidomide and rituximab) consists of 3 step-up doses.

EPKINLY as Monotherapy:

Administer EPKINLY in 28-day cycles until disease progression or unacceptable toxicity.

Table 1: EPKINLY Dosage Schedule for Patients with DLBCL or High-grade B-cell Lymphoma

Indication	Cycle[a]	Day	Dose of EPKINLY	
DLBCL or 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	
	Cycle 10 and beyond	1	48 mg	
[a] Cycle = 28 days.				

Table 2: EPKINLY Dosage Schedule for Patients with FL when Given as Monotherapy

Indication	Cycle[a]	Day	Dose of EPKINLY	
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
	Cycles 2 and 3	1, 8, 15 and 22	48 mg	
	Cycles 4 to 9	1 and 15	48 mg	
	Cycle 10 and beyond	1	48 mg	
[a] Cycle = 28 days.				

EPKINLY in Combination with Lenalidomide and Rituximab:

Administer EPKINLY in 28-day cycles for a total of 12 cycles or until disease progression or unacceptable toxicity, whichever occurs first.

Table 3: EPKINLY Dosage Schedule in Combination with Lenalidomide and Rituximab for Patients with FL

Indication	Cycle[a]	Day	Dose of EPKINLY	
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
	Cycles 2 and 3	1, 8, 15, and 22	48 mg	
	Cycles 4 to 12	1	48 mg	
[a] Cycle = 28 days.				

Administer EPKINLY in combination with lenalidomide 20 mg (Days 1 to 21 in Cycles 1 to 12) and rituximab 375 mg/m^2 (Cycles 1 to 5) *[see Clinical Studies (14.2)]*. Refer to the lenalidomide prescribing information and rituximab prescribing information for the respective dosage recommendations, including lenalidomide dosage recommendations for patients with renal insufficiency.

2.3 Restarting EPKINLY after Dosage Delay

If a dose of EPKINLY is delayed, restart therapy based on the recommendations made in Table 4 for patients with DLBCL or high-grade B-cell lymphoma, or Table 5 for patients with FL *[see Dosage and Administration (2.2)]*.

Table 4: Recommendations for Restarting EPKINLY After Dosage Delay for Patients with DLBCL or High-grade B-cell Lymphoma

Last Dose Administered	Time Since the Last Dose Administered	Action for Next Dose(s)[a]
0.16 mg (e.g., 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 (e.g., 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 (e.g., 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 EPKINLY dose and monitor patients accordingly *[see Dosage and Administration (2.4, 2.6)]*.

Table 5: Recommendations for Restarting EPKINLY After Dosage Delay for Patients with FL

Last Dose Administered	Time Since the Last Dose Administered	Action for Next Dose(s)[a]
0.16 mg (e.g., 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 (e.g., 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.

Last Dose Administered	Time Since the Last Dose Administered	Action for Next Dose(s)[a]
3 mg (e.g., 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 (e.g., 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 EPKINLY dose and monitor patients accordingly *[see Dosage and Administration (2.4, 2.6)]*.		

2.4 Recommended Pre- and Post-Administration Medications

Administer pre- and post-administration medications as outlined in Table 6 to reduce the risk of CRS *[see Warnings and Precautions (5.1)]*.

Table 6: EPKINLY Pre- and Post-Administration Medications

Cycle	Patients requiring medication	Medication	Administration
Cycle 1	All patients	• Dexamethasone[a] (15 mg oral or intravenous) or Prednisolone (100 mg oral or intravenous) or equivalent	• 30-120 minutes prior to each weekly administration of EPKINLY • And for three consecutive days following each weekly administration of EPKINLY in Cycle 1
		• Diphenhydramine (50 mg oral or intravenous) or equivalent • Acetaminophen (650 mg to 1,000 mg oral)	• 30-120 minutes prior to each weekly administration of EPKINLY

Cycle	Patients requiring medication	Medication	Administration
Cycle 2+	Patients who experienced Grade 2 or 3[b] CRS with previous dose	• Dexamethasone[a] (15 mg oral or intravenous) or Prednisolone (100 mg oral or intravenous) or equivalent	• 30-120 minutes prior to next administration of EPKINLY after a Grade 2 or 3[b] CRS event • And for three consecutive days following the next administration of EPKINLY until EPKINLY is given without subsequent CRS of Grade 2 or higher
[a] Dexamethasone is the preferred corticosteroid when available. [b] Patients will be permanently discontinued from EPKINLY after Grade 4 CRS.			

2.5 Recommended Prophylaxis

Pneumocystis jirovecii pneumonia (PJP)
Provide PJP prophylaxis during treatment with EPKINLY.

Herpesvirus
Consider providing prophylaxis against herpesvirus during treatment with EPKINLY to prevent herpes simplex and herpes zoster.

Thromboprophylaxis
Refer to the lenalidomide prescribing information for recommendations on prophylaxis for venous and arterial thrombotic events.

2.6 Dosage Modifications and Management of Adverse Reactions

See Tables 7 and 8 for recommended actions for adverse reactions of CRS and ICANS, respectively. See Tables 9 and 10 for recommended actions for other adverse reactions following administration of EPKINLY given as monotherapy and in combination with lenalidomide and rituximab, respectively.

Cytokine Release Syndrome (CRS)
Identify CRS based on clinical presentation *[see Warnings and Precautions (5.1)]*. Evaluate for and treat other causes of fever, hypotension, and hypoxia.

If CRS is suspected, withhold EPKINLY until CRS resolves. Manage according to the recommendations in Table 7 and consider further management per current practice guidelines. Administer supportive therapy for CRS, which may include intensive care for severe or life-threatening CRS.

Table 7: Recommendations for Management of Cytokine Release Syndrome

Grade[a]	Presenting Symptoms	Actions
Grade 1	Temperature ≥ 100.4°F (38°C)[b]	• Withhold EPKINLY and manage per current practice guidelines. • Ensure CRS symptoms are resolved prior to next dose of EPKINLY.[c]
Grade 2	Temperature ≥ 100.4°F (38°C)[b] with: Hypotension not requiring vasopressors and/or Hypoxia requiring low-flow oxygen[e] by nasal cannula or blow-by.	• Withhold EPKINLY and manage per current practice guidelines. • Ensure CRS symptoms are resolved prior to next dose of EPKINLY.[c] • Administer premedication[d] prior to next dose of EPKINLY. • For the next dose of EPKINLY, monitor more frequently and consider hospitalization.
Grade 3	Temperature ≥ 100.4°F (38°C)[b] with: Hypotension requiring a vasopressor (with or without vasopressin) and/or Hypoxia requiring high-flow oxygen[e] by nasal cannula, face mask, non-rebreather mask, or Venturi mask.	• Withhold EPKINLY and manage per current practice guidelines, which may include intensive care. • Ensure CRS symptoms are resolved prior to the next dose of EPKINLY.[c] • Administer premedication[d] prior to next dose of EPKINLY. • Hospitalize for the next dose of EPKINLY.
		Recurrent Grade 3 CRS • Permanently discontinue EPKINLY. • Manage CRS per current practice guidelines and provide supportive therapy, which may include intensive care.
Grade 4	Temperature ≥ 100.4°F (38°C)[b] with: Hypotension requiring multiple vasopressors (excluding vasopressin) and/or Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation).	• Permanently discontinue EPKINLY. • Manage CRS per current practice guidelines and provide supportive therapy, which may include intensive care.

Grade[a]	Presenting Symptoms	Actions
[a] Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for CRS. [b] Premedication may mask fever, therefore if clinical presentation is consistent with CRS, follow these management guidelines. [c] Refer to Table 4 or Table 5 for information on restarting EPKINLY after dosage delays *[see Dosage and Administration (2.3)]*. [d] If Grade 2 or 3 CRS occurs with the second full dose (48 mg) or beyond, administer CRS pre- and post-administration medications with each subsequent dose until a EPKINLY dose is given without subsequent CRS of Grade 2 or higher. Refer to Table 6 for additional information on pre- and post-administration medications. [e] Low-flow oxygen defined as oxygen delivered at < 6L/minute; high-flow oxygen defined as oxygen delivered at ≥ 6 L/minute.		

Immune Effector Cell-Associated Neurological Toxicity Syndrome (ICANS)

Monitor patients for signs and symptoms of ICANS *[see Warnings and Precautions (5.2)]*. At the first sign of ICANS, withhold EPKINLY and consider neurology evaluation. Rule out other causes of neurologic symptoms. Provide supportive therapy, which may include intensive care, for ICANS *[see Warnings and Precautions (5.2)]*. Manage ICANS according to the recommendations in Table 8 and consider further management per current practice guidelines.

Table 8: Recommendations for Management of Immune Effector Cell-Associated Neurotoxicity Syndrome

Grade[a]	Presenting Symptoms[b]	Actions
Grade 1	ICE score 7-9[c], Or depressed level of consciousness[d]: awakens spontaneously.	• Withhold EPKINLY until ICANS resolves.[e] • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis.
Grade 2	ICE score 3-6[c], Or depressed level of consciousness[d]: awakens to voice.	• Withhold EPKINLY until ICANS resolves.[e] • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis.

Grade[a]	Presenting Symptoms[b]	Actions
Grade 3	ICE score 0-2[c], Or depressed level of consciousness[d]: awakens only to tactile stimulus, Or seizures,[d] either: • Any clinical seizure, focal or generalized, that resolves rapidly, or • Non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, Or raised intracranial pressure: focal/local edema on neuroimaging.[d]	First Occurrence of Grade 3 ICANS • Withhold EPKINLY until ICANS resolves.[e] • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • Provide supportive therapy, which may include intensive care.
		Recurrent Grade 3 ICANS • Permanently discontinue EPKINLY • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • Provide supportive therapy, which may include intensive care.
Grade 4	ICE score 0[c], Or depressed level of consciousness[d]: either: • Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • Stupor or coma Or seizures,[d] either: • Life-threatening prolonged seizure (> 5 minutes), or • Repetitive clinical or electrical seizures without return to baseline in between,	• Permanently discontinue EPKINLY. • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Alternatively, consider administration of methylprednisolone 1,000 mg per day intravenously and continue methylprednisolone 1,000 mg per day intravenously for 2 or more days.

Grade[a]	Presenting Symptoms[b]	Actions
	Or motor findings[d]: • Deep focal motor weakness, such as hemiparesis or paraparesis, or raised intracranial pressure/cerebral edema,[d] with signs/symptoms such as: • Diffuse cerebral edema on neuroimaging, or • Decerebrate or decorticate posturing, or • Cranial nerve VI palsy, or • Papilledema, or • Cushing's triad.	• Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • Provide supportive therapy, which may include intensive care.

[a] Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for ICANS.
[b] Management is determined by the most severe event, not attributable to any other cause.
[c] If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: Orientation (oriented to year, month, city, hospital = 4 points); Naming (names 3 objects, e.g., point to clock, pen, button = 3 points); Following Commands (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); Writing (ability to write a standard sentence = 1 point); and Attention (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points.
[d] Not attributable to any other cause.
[e] See Table 4 or Table 5 for recommendations on restarting EPKINLY after dosage delays *[see Dosage and Administration (2.3)]*.
[f] All references to dexamethasone administration are dexamethasone or equivalent.

Table 9: Recommended Dosage Modifications for Other Adverse Reactions when EPKINLY is Given as Monotherapy

Adverse Reaction	Severity[1]	Action
Infections *[see Warnings and Precautions (5.3)]*	Grades 1-4	• Withhold EPKINLY in patients with active infection, until the infection resolves.[2] • For Grade 4, consider permanent discontinuation of EPKINLY.
Neutropenia *[see Warnings and Precautions (5.4)]*	Absolute neutrophil count less than 0.5 x 10^9/L	• Withhold EPKINLY until absolute neutrophil count is 0.5 x 10^9/L or higher.[2]
Thrombocytopenia *[see Warnings and Precautions (5.4)]*	Platelet count less than 50 x 10^9/L	• Withhold EPKINLY until platelet count is 50 x 10^9/L or higher.[2]

Adverse Reaction	Severity[1]	Action
Other Adverse Reactions *[see Adverse Reactions (6.1)]*	Grade 3 or higher	• Withhold EPKINLY until the toxicity resolves to Grade 1 or baseline.[2]

[1] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0.
[2] See Table 4 or Table 5 for recommendations on restarting EPKINLY after dosage delays *[see Dosage and Administration (2.3)]*.

Table 10: Recommended Dosage Modifications for Other Adverse Reactions when EPKINLY is Given in Combination with Lenalidomide and Rituximab

Adverse Reaction	Severity[1]	Action[2]
Neutropenia *[see Warnings and Precautions (5.4)]*	Absolute neutrophil count less than 0.5 x 10^9/L	• Consider G-CSF. • Withhold EPKINLY until absolute neutrophil count is 1 x 10^9/L or higher.[3] • Withhold lenalidomide for remainder of cycle. On Day 1 of next cycle, the dose of lenalidomide may be maintained if neutropenia was the only toxicity limiting lenalidomide dosing.
Febrile Neutropenia *[see Warnings and Precautions (5.4)]*	Grade 3 or higher	• Consider G-CSF. • Withhold EPKINLY until fever resolves and absolute neutrophil count is 1 x 10^9/L or higher.[3] • Withhold lenalidomide for remainder of cycle. On Day 1 of next cycle, dose of lenalidomide may be maintained if febrile neutropenia was the only toxicity limiting lenalidomide dosing.
Thrombocytopenia *[see Warnings and Precautions (5.4)]*	Platelet count less than 50 x 10^9/L	• Withhold EPKINLY until platelet count is 50 x 10^9/L or higher.[3] • Withhold lenalidomide for remainder of cycle. Decrease lenalidomide dose for next cycle.
Other Adverse Reactions *[see Adverse Reactions (6.1)]*	Grade 3	• For first episode, withhold EPKINLY until improvement

Adverse Reaction	Severity[1]	Action[2]
		to Grade 2 or less or resolution to baseline.[3] • For second episode, permanently discontinue EPKINLY if clinically indicated.[3]
	Grade 4	• Permanently discontinue EPKINLY at discretion of healthcare provider.

[1] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0.
[2] Refer to lenalidomide prescribing information for additional toxicity guidelines.
[3] See Table 4 or 5 for recommendations on restarting EPKINLY after dosage delays *[see Dosage and Administration (2.3)].*

2.7 Preparation of Diluted EPKINLY using the Vial Method

Read this entire section carefully before preparation of EPKINLY. Certain doses of EPKINLY require **dilution** prior to administration. Follow the preparation instructions provided below, as improper preparation may lead to improper dose. This section describes preparation of diluted EPKINLY using empty sterile vial method. For preparation using sterile syringe method, see subsection 2.8 *[see Dosage and Administration (2.8)]*.

EPKINLY is prepared and administered by a healthcare provider as a subcutaneous injection. The administration of EPKINLY takes place over the course of 28-day cycles, following the step-up dosage schedule in Section 2.2.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Use aseptic technique to prepare EPKINLY. Filtration of the diluted solution is not required.

*0.16 mg Dose Preparation Instructions (**2 dilutions required**) – Empty Sterile Vial Method*
Use an appropriately sized syringe, vial, and needle for each transfer step.

1. Prepare EPKINLY vial a. Retrieve one 4 mg/0.8 mL EPKINLY vial from the refrigerator. b. Allow the vial to come to room temperature for no more than 1 hour. c. Gently swirl the EPKINLY vial. **DO NOT** invert, vortex, or vigorously shake the vial.
2. Perform first dilution a. Label an appropriately sized empty vial as **"Dilution A."** b. Transfer **0.8 mL of EPKINLY** into the **Dilution A** vial.

c. Transfer **4.2 mL of 0.9% Sodium Chloride Injection** into the **Dilution A** vial. The initially diluted solution contains 0.8 mg/mL of EPKINLY. d. Gently swirl the **Dilution A** vial for 30 to 45 seconds.
3. Perform second dilution a. Label an appropriately sized empty vial as **"Dilution B."** b. Transfer **2 mL of solution** from the **Dilution A** vial into the **Dilution B** vial. The **Dilution A** vial is no longer needed. c. Transfer **8 mL of 0.9% Sodium Chloride Injection** into the **Dilution B** vial to make a final concentration of 0.16 mg/mL. d. Gently swirl the **Dilution B** vial for 30 to 45 seconds.
4. Withdraw dose a. Withdraw **1 mL of the diluted EPKINLY** from the **Dilution B** vial into a syringe.
5. Label syringe a. Label the syringe with the dose strength (0.16 mg) and the time of day.

Discard the vial containing unused EPKINLY.

*0.8 mg Dose Preparation Instructions (**1 dilution required**) – Empty Sterile Vial Method*
Use an appropriately sized syringe, vial, and needle for each transfer step.

1. Prepare EPKINLY vial a. Retrieve one 4 mg/0.8 mL EPKINLY vial from the refrigerator. b. Allow the vial to come to room temperature for no more than 1 hour. c. Gently swirl the EPKINLY vial. **DO NOT** invert, vortex, or vigorously shake the vial.
2. Perform dilution a. Label an appropriately sized empty vial as "**Dilution A**". b. Transfer **0.8 mL of EPKINLY** into the **Dilution A** vial. c. Transfer **4.2 mL of 0.9% Sodium Chloride Injection** into the **Dilution A** vial to make a final concentration of 0.8 mg/mL. d. Gently swirl the **Dilution A** vial for 30 to 45 seconds.
3. Withdraw dose a. Withdraw **1 mL of the diluted EPKINLY** from the **Dilution A** vial into a syringe.
4. Label syringe a. Label the syringe with the dose strength (0.8 mg) and the time of day.

Discard the vial containing unused EPKINLY.

2.8 Preparation of Diluted EPKINLY using the Syringe Method

Read this entire section carefully before preparation of EPKINLY. Certain doses of EPKINLY require **dilution** prior to administration. Follow the preparation instructions provided below, as improper preparation may lead to improper dose.

EPKINLY is prepared and administered by a healthcare provider as a subcutaneous injection. The administration of EPKINLY takes place over the course of 28-day cycles, following the step-up dosage schedule in Section 2.2.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Use aseptic technique to prepare EPKINLY. Filtration of the diluted solution is not required.

*0.16 mg Dose Preparation Instructions (**2 dilutions required**) – Sterile Syringe Method*
Use an appropriately sized syringe and needle for each transfer step.

1. Prepare EPKINLY vial a. Retrieve one 4 mg/0.8 mL EPKINLY vial from the refrigerator. b. Allow the vial to come to room temperature for no more than 1 hour. c. Gently swirl the EPKINLY vial. **DO NOT** invert, vortex, or vigorously shake the vial.
2. Perform first dilution a. Label an appropriately sized syringe as **"Dilution A."** b. Withdraw **4.2 mL of 0.9% Sodium Chloride Injection** into the **Dilution A** syringe. Include approximately 0.2 mL air in the syringe. c. In a new syringe labeled as **"Syringe 1"**, withdraw **0.8 mL of EPKINLY**. d. Connect the two syringes and push the **0.8 mL of EPKINLY** into the **Dilution A** syringe. The initially diluted solution contains 0.8 mg/mL of EPKINLY e. Gently mix by inverting the connected syringes 180 degrees 5 times. f. Disconnect the syringes and discard **Syringe 1**.
3. Perform second dilution a. Label an appropriately sized syringe as **"Dilution B."** b. Withdraw **8 mL of 0.9% Sodium Chloride Injection** into the **Dilution B** syringe. Include approximately 0.2 mL air in the syringe. c. Label another appropriately sized syringe as **"Syringe 2."** d. Connect **Syringe 2** to the **Dilution A** syringe and transfer **2 mL of solution** into **Syringe 2**. The **Dilution A** syringe is no longer needed. e. Connect **Syringe 2** to the **Dilution B** syringe and push the **2 mL of solution** into the **Dilution B** syringe to make a final concentration of 0.16 mg/mL.

f. Gently mix by inverting the connected syringes 180 degrees 5 times. g. Disconnect the syringes and discard **Syringe 2**.
4. Withdraw dose a. Connect and transfer **1 mL of the diluted EPKINLY** from the **Dilution B** syringe into a new syringe. The **Dilution B** syringe is no longer needed.
5. Label syringe a. Label the syringe with the dose strength (0.16 mg) and the time of day.

Discard the vial containing unused EPKINLY.

*0.8 mg Dose Preparation Instructions (**1 dilution required**) – Sterile Syringe Method*
Use an appropriately sized syringe and needle for each transfer step.

1. Prepare EPKINLY vial a. Retrieve one 4 mg/0.8 mL EPKINLY vial from the refrigerator. b. Allow the vial to come to room temperature for no more than 1 hour. c. Gently swirl the EPKINLY vial. **DO NOT** invert, vortex, or vigorously shake the vial.
2. Perform dilution a. Label an appropriately sized syringe as **"Dilution A."** b. Withdraw **4.2 mL of 0.9% Sodium Chloride Injection** into the **Dilution A** syringe. Include approximately 0.2 mL air in the syringe. c. In a new syringe labeled as "**Syringe 1**", withdraw **0.8 mL of EPKINLY**. d. Connect the two syringes and push the **0.8 mL of EPKINLY** into the **Dilution A** syringe to make a final concentration of 0.8 mg/mL. e. Gently mix by inverting the connected syringes 180 degrees 5 times. f. Disconnect the syringes and discard **Syringe 1**.
3. Withdraw dose a. Connect a new syringe to the **Dilution A** syringe and transfer **1 mL of the diluted EPKINLY** into the new syringe. The **Dilution A** syringe is no longer needed.
4. Label syringe a. Label the syringe with the dose strength (0.8 mg) and the time of day.

Discard the vial containing unused EPKINLY.

2.9 Preparation of 3 mg and 48 mg EPKINLY Doses

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Use aseptic technique to prepare EPKINLY.

3 mg Dose Preparation Instructions ***(No dilution required)***
EPKINLY 3 mg dose is required for patients with FL only *[see Dosage and Administration (2.2)]*.

1. Prepare EPKINLY vial a. Retrieve one 4 mg/0.8 mL EPKINLY vial from the refrigerator. b. Allow the vial to come to room temperature for no more than 1 hour. c. Gently swirl the EPKINLY vial. **DO NOT** invert, vortex, or vigorously shake the vial.
2. Withdraw dose a. Withdraw **0.6 mL of EPKINLY** into a syringe.
3. Label syringe a. Label the syringe with the dose strength (3 mg) and the time of day.

Discard the vial containing unused EPKINLY.

*48 mg Dose Preparation Instructions (**No dilution required**)*
EPKINLY 48 mg/0.8 mL vial is supplied as ready-to-use solution that does not need dilution prior to administration.

1. Prepare EPKINLY vial a. Retrieve one 48 mg/0.8 mL EPKINLY vial from the refrigerator. b. Allow the vial to come to room temperature for no more than 1 hour. c. Gently swirl the EPKINLY vial. **DO NOT** invert, vortex, or vigorously shake the vial.
2. Withdraw dose a. Withdraw **0.8 mL of EPKINLY** into a syringe.
3. Label syringe a. Label the syringe with the dose strength (48 mg) and the time of day.

Discard the vial containing unused EPKINLY.

2.10 Storage and Administration

Storage of EPKINLY Solution in the Syringe
Use EPKINLY solution in the syringe immediately. If not used immediately, store the solution refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours or at room temperature at 20°C to

25°C (68°F to 77°F) for up to 12 hours. The total storage time from the start of dose preparation to administration should not exceed 24 hours. Protect from direct sunlight. Discard unused EPKINLY solution beyond the allowable storage time.

Administration of EPKINLY
To minimize injection pain, allow EPKINLY solution to equilibrate to room temperature for no more than 1 hour before administration. Inject the required volume of EPKINLY 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.

3 DOSAGE FORMS AND STRENGTHS

EPKINLY is a clear to slightly opalescent, colorless to slightly yellow solution for subcutaneous injection:

- Injection: 4 mg/0.8 mL in a single-dose vial
- Injection: 48 mg/0.8 mL in a single-dose vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome

EPKINLY can cause CRS, including serious or fatal reactions *[see Adverse Reactions (6.1)]*.

Relapsed or Refractory Large B-cell Lymphoma
CRS occurred in 51% (80/157) of patients with LBCL receiving EPKINLY at the recommended dosage schedule in EPCORE NHL-1, with Grade 1 CRS occurring in 37%, Grade 2 in 17%, and Grade 3 in 2.5% of patients. Recurrent CRS occurred in 31% of these patients. Most CRS events (92%) occurred during Cycle 1. In Cycle 1, CRS events occurred in 6% of patients after the 0.16 mg dose, 12% after the 0.8 mg dose, 43% after the first 48 mg dose, and 5% after the next 48 mg dose. The median time to onset of CRS from the most recent EPKINLY dose was 24 hours (range: 0 to 10 days). The median time to onset after the first 48 mg dose was 21 hours (range: 0 to 7 days).

For patients with LBCL, assess whether hospitalization or outpatient monitoring for the first 48 mg dose (Cycle 1 Day 15) is appropriate based on comorbidities or other situational factors *[see*

Dosage and Administration (2.1)]. During outpatient monitoring after the first 48 mg dose, patients should remain in proximity to a healthcare facility that can assess and manage CRS.

Relapsed or Refractory Follicular Lymphoma

CRS occurred in 49% (42/86) of patients with FL receiving EPKINLY monotherapy at the recommended dosage schedule in EPCORE NHL-1, with Grade 1 CRS occurring in 45% and Grade 2 in 9% of patients. Recurrent CRS occurred in 48% of patients. Most CRS events (88%) occurred during Cycle 1. In Cycle 1, CRS events occurred in 12% of patients after the 0.16 mg dose, 6% after the 0.8 mg dose, 15% after the 3 mg dose, and 37% after the first 48 mg dose. The median time to onset of CRS from the most recent EPKINLY dose was 59 hours (range: 0.1 to 7 days). The median time to onset after the first 48 mg dose was 61 hours (range: 0.1 to 7 days).

CRS occurred in 24% (32/131) of patients with FL receiving EPKINLY at the recommended dosage schedule in combination with lenalidomide and rituximab in EPCORE FL-1, with Grade 1 CRS occurring in 19%, Grade 2 in 5% of patients, and serious adverse reactions due to CRS in 12%. Recurrent CRS occurred in 41% of patients. Most CRS events (88%) occurred during Cycle 1. In Cycle 1, CRS occurred in 5% of patients after the 0.16 mg dose, 3.8% after the 0.8 mg dose, 2.3% after the 3 mg dose, and 18% after the first 48 mg dose. The median time to onset of CRS from the most recent EPKINLY dose was 78 hours (range: 0.2 to 12 days). The median time to onset after the first 48 mg dose was 41 hours (range: 0.3 to 12 days).

For patients with FL, assess whether hospitalization or outpatient monitoring for the first 48 mg dose (Cycle 1 Day 22) is appropriate based on comorbidities or other situational factors *[see Dosage and Administration (2.1)]*. During outpatient monitoring after the first 48 mg dose, patients should remain in proximity to a healthcare facility that can assess and manage CRS.

Among patients with LBCL or FL who experienced CRS, signs and symptoms included pyrexia, hypotension, hypoxia, dyspnea, chills, and tachycardia. CRS resolved in 98% of patients, after a median duration of 2 days (range: < 1 to 27 days). Concurrent neurological adverse reactions associated with CRS occurred in 2.5% of patients with LBCL, 4.7% of patients with FL receiving EPKINLY monotherapy, and 1.5% of patients receiving EPKINLY in combination with lenalidomide and rituximab. Concurrent neurological adverse reactions included headache, confusional state, tremors, dizziness, and ataxia.

Initiate EPKINLY according to the recommended step-up dosage schedule. Administer pretreatment medications to reduce the risk of CRS and monitor patients for potential CRS accordingly *[see Dosage and Administration (2.2, 2.3, 2.4)]*. At the first signs or symptoms of CRS, immediately evaluate patients for hospitalization, manage per current practice guidelines, and administer supportive care as appropriate. Withhold or discontinue EPKINLY based on the severity of CRS *[see Dosage and Administration (2.6)]*.

Patients who experience CRS (or other adverse reactions that impair consciousness) should be evaluated and advised not to drive and to refrain from operating heavy or potentially dangerous machinery until resolution.

5.2 Immune Effector Cell-Associated Neurotoxicity Syndrome

EPKINLY can cause life-threatening and fatal immune effector cell-associated neurotoxicity syndrome (ICANS) *[see Adverse Reactions (6.1)]*.

Relapsed or Refractory Large B-cell Lymphoma
ICANS occurred in 6% (10/157) of patients with LBCL receiving EPKINLY at the recommended dosage schedule in EPCORE NHL-1, with Grade 1 ICANS in 4.5% and Grade 2 ICANS in 1.3% of patients. There was one (0.6%) fatal ICANS occurrence. Of the 10 ICANS events, 9 occurred within Cycle 1 of EPKINLY treatment, with a median time to onset of ICANS of 16.5 days (range: 8 to 141 days) from the start of treatment. Relative to the most recent administration of EPKINLY, the median time to onset of ICANS was 3 days (range: 1 to 13 days). The median duration of ICANS was 4 days (range: 0 to 8 days) with ICANS resolving in 90% of patients with supportive care.

Relapsed or Refractory Follicular Lymphoma
ICANS occurred in 6% (8/127) of patients with FL receiving EPKINLY monotherapy following the 2-step up dosage schedule in EPCORE NHL-1, with Grade 1 ICANS in 3.9% and Grade 2 ICANS in 2.4% of patients. The median time to onset of ICANS was 22 days (range: 14 to 66 days) from the start of treatment. Relative to the most recent administration of EPKINLY, the median time to onset of ICANS was 3 days (range: 0.4 to 7 days). The median duration of ICANS was 2 days (range: 1 to 7 days) with ICANS resolving in 100% of patients.

Among patients with FL who received EPKINLY at the recommended dosage schedule in combination with lenalidomide and rituximab in EPCORE FL-1, ICANS occurred in 0.8% (1/131, Grade 1).

For patients with LBCL or FL, clinical manifestations of ICANS included, but were not limited to confusional state, lethargy, tremor, dysgraphia, aphasia, and non-convulsive status epilepticus. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. Monitor patients for potential ICANS following EPKINLY. At the first signs or symptoms of ICANS, immediately evaluate patient and provide supportive therapy based on severity. Withhold or discontinue EPKINLY per recommendations and consider further management per current practice guidelines *[see Dosage and Administration (2.6)]*.

Patients who experience signs or symptoms of ICANS or any other adverse reactions that impair cognition or consciousness should be evaluated, including potential neurology evaluation, and patients at increased risk should be advised not to drive and to refrain from operating heavy or potentially dangerous machinery until resolution.

5.3 Infections

EPKINLY can cause fatal and serious infections *[see Adverse Reactions (6.1)]*.

Serious infections, including opportunistic infections, were reported in 15% of patients with LBCL receiving EPKINLY at the recommended dosage schedule in EPCORE NHL-1 and were

most commonly due to sepsis (4.5%) and pneumonia (3.2%). Fatal infections occurred in 1.3% of patients and were due to COVID-19.

Serious infections, including opportunistic infections, were reported in 40% of patients with FL receiving EPKINLY monotherapy following the 2-step up dosage schedule in EPCORE NHL-1 and were most commonly due to COVID-19 (20%), pneumonia (13%), and urinary tract infections (3%). Fatal infections occurred in 6% of patients and included COVID-19 (5%), pneumonia (0.8%), and sepsis (0.8%).

Among 243 patients with FL who received EPKINLY in combination with lenalidomide and rituximab in EPCORE FL-1, serious infections occurred in 28% of patients. The most common serious infections were pneumonia (15%), COVID-19 (7%), opportunistic infections (5%) and upper respiratory infections (3.3%). The most common opportunistic infections of any grade were CMV infection (7%) and herpesvirus infection (7%).

Progressive multifocal leukoencephalopathy (PML), including fatal cases, has occurred in patients treated with EPKINLY. Across a broader clinical trial population, PML was reported in 0.4% (11/3072) of patients, including in the first-line treatment setting. Of the 11 cases of PML, six resulted in fatal outcomes and one was unresolved at the time of death.

Monitor patients for signs and symptoms of infection and treat appropriately. Avoid administration of EPKINLY in patients with active infections. Provide PJP prophylaxis during treatment with EPKINLY, and consider initiating prophylaxis against herpesvirus *[see Dosage and Administration (2.5)]*.

Consider monitoring immunoglobulin levels during treatment and administration of immunoglobulin treatment as appropriate.

Withhold or consider permanent discontinuation of EPKINLY based on severity *[see Dosage and Administration (2.6)]*.

5.4 Cytopenias

EPKINLY can cause serious or severe cytopenias, including neutropenia, lymphopenia, anemia, and thrombocytopenia *[see Adverse Reactions (6.1)]*.

In patients with LBCL who received EPKINLY at the recommended dosage schedule, Grade 3 or 4 decreased neutrophils occurred in 32% (Grade 4, 14%), decreased hemoglobin in 12% (Grade 4, 0%), and decreased platelets in 12% (Grade 4, 7%) of patients. Febrile neutropenia occurred in 2.5% (Grade 4, 0.6%).

In patients with FL who received EPKINLY monotherapy following the 2-step up dosage schedule, Grade 3 or 4 decreased neutrophils occurred in 30% (Grade 4, 17%), decreased hemoglobin in 10% (Grade 4, 0%), and decreased platelets in 8% of patients (Grade 4, 4%). Febrile neutropenia occurred in 3.1% (Grade 4, 0%).

In patients with FL who received EPKINLY in combination with lenalidomide and rituximab, Grade 3 or 4 decreased neutrophils occurred in 67% (Grade 4, 41%), decreased lymphocytes in 62% (Grade 4, 13%), decreased hemoglobin in 7%, and decreased platelets in 10% (Grade 4, 4.1%) of patients. Febrile neutropenia occurred in 6% (Grade 4, 2.1%).

Monitor complete blood counts throughout treatment. Based on the severity of cytopenias, temporarily withhold or permanently discontinue EPKINLY *[see Dosage and Administration (2.6)]*. Consider prophylactic granulocyte colony-stimulating factor administration as applicable.

5.5 Embryo-Fetal Toxicity

Based on its mechanism of action, EPKINLY may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with EPKINLY and for 4 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Cytokine Release Syndrome *[see Warnings and Precautions (5.1)]*.
- Immune Effector Cell-Associated Neurotoxicity Syndrome *[see Warnings and Precautions (5.2)]*.
- Infections *[see Warnings and Precautions (5.3)]*.
- Cytopenias *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Relapsed or Refractory Large B-cell Lymphoma (LBCL)

EPCORE NHL-1

The safety of EPKINLY was evaluated in EPCORE NHL-1, a single-arm study of patients with relapsed or refractory LBCL after two or more lines of systemic therapy, including DLBCL not otherwise specified, DLBCL arising from indolent lymphoma, high grade B-cell lymphoma, and other B-cell lymphomas *[see Clinical Studies (14.1)]*. A total of 157 patients with LBCL received EPKINLY via subcutaneous injection until disease progression or unacceptable toxicities according to the following 28-day cycle schedule:

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

Of the 157 patients treated, the median age was 64 years (range: 20 to 83), 60% were male, and 97% had an ECOG performance status of 0 or 1. Race was reported in 133 (85%) patients; of these patients, 61% were White, 19% were Asian, and 0.6% were Native Hawaiian or Other Pacific Islander. There were no Black or African American or Hispanic or Latino patients treated in the clinical trial as reported. The median number of prior therapies was 3 (range: 2 to 11). The study excluded patients with CNS involvement of lymphoma, allogeneic HSCT or solid organ transplant, an ongoing active infection, and any patients with known impaired T-cell immunity.

The median duration of exposure for patients receiving EPKINLY was 5 cycles (range: 1 to 20 cycles).

Serious adverse reactions occurred in 54% of patients who received EPKINLY. Serious adverse reactions in ≥ 2% of patients included CRS, infections (including sepsis, COVID-19, pneumonia, and upper respiratory tract infections), pleural effusion, febrile neutropenia, fever, and ICANS. Fatal adverse reactions occurred in 3.8% of patients who received EPKINLY, including COVID-19 (1.3%), hepatotoxicity (0.6%), ICANS (0.6%), myocardial infarction (0.6%), and pulmonary embolism (0.6%).

Permanent discontinuation of EPKINLY due to an adverse reaction occurred in 3.8% of patients. Adverse reactions which resulted in permanent discontinuation of EPKINLY included COVID-19, CRS, ICANS, pleural effusion, and fatigue.

Dosage interruptions of EPKINLY due to an adverse reaction occurred in 34% of patients who received EPKINLY. Adverse reactions which required dosage interruption in ≥ 3% of patients included CRS, neutropenia, sepsis, and thrombocytopenia.

The most common (≥ 20%) adverse reactions were CRS, fatigue, musculoskeletal pain, injection site reactions, pyrexia, abdominal pain, nausea, and diarrhea. The most common Grade 3 to 4 laboratory abnormalities (≥ 10%) were decreased lymphocyte count, decreased neutrophil count, decreased white blood cell count, decreased hemoglobin, and decreased platelets.

Table 11 summarizes the adverse reactions in EPCORE NHL-1.

Table 11: Adverse Reactions (≥ 10%) in Patients with Relapsed or Refractory LBCL Who Received EPKINLY in EPCORE NHL-1

Adverse Reaction[§]	EPKINLY (N=157)	
	All Grades (%)	Grade 3 or 4 (%)
Immune system disorders		
Cytokine release syndrome[*]	51	2.5[#]
General disorders and administration site conditions		
Fatigue[a]	29	2.5[#]
Injection site reactions[b]	27	0
Pyrexia	24	0

Adverse Reaction[§]	EPKINLY (N=157)	
	All Grades (%)	Grade 3 or 4 (%)
Edema[c]	14	1.9[#]
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[d]	28	1.3[#]
Gastrointestinal disorders		
Abdominal pain[e]	23	1.9[#]
Diarrhea	20	0
Nausea	20	1.3[#]
Vomiting	12	0.6[#]
Skin and subcutaneous disorders		
Rash[f]	15	0.6[#]
Nervous system disorder		
Headache	13	0.6[#]
Metabolism and nutrition disorders		
Decreased appetite	12	0.6[#]
Cardiac disorders		
Cardiac arrhythmias[g]	10	0.6[#]

[§] Adverse reactions were graded based on CTCAE Version 5.0
[#] Only grade 3 adverse reactions occurred.
[*] CRS was graded using ASTCT consensus criteria (Lee et al., 2019).
[a] Fatigue includes asthenia, fatigue, lethargy.
[b] Injection site reaction includes injection site erythema, injection site hypertrophy, injection site inflammation, injection site mass, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, injection site urticaria.
[c] Edema includes edema, edema peripheral, face edema, generalized edema, peripheral swelling.
[d] Musculoskeletal pain includes back pain, bone pain, flank pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain, pain in extremity, spinal pain.
[e] Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness.
[f] Rash includes dermatitis bullous, erythema, palmar erythema, penile erythema, rash, rash erythematous, rash maculo-papular, rash pustular, recall phenomenon, seborrheic dermatitis, skin exfoliation.
[g] Cardiac arrhythmias includes bradycardia, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, tachycardia.

Clinically relevant adverse reactions in < 10% of patients who received EPKINLY included ICANS, sepsis, pleural effusion, COVID-19, pneumonia (including pneumonia and COVID-19 pneumonia), tumor flare, febrile neutropenia, upper respiratory tract infections, and tumor lysis syndrome.

Table 12 summarizes laboratory abnormalities in EPCORE NHL-1.

Table 12: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients with Relapsed or Refractory LBCL Who Received EPKINLY in EPCORE NHL-1

Laboratory Abnormality*	EPKINLY[1]	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Lymphocyte count decreased	87	77
Hemoglobin decreased	62	12
White blood cells decreased	53	22
Neutrophils decreased	50	32
Platelets decreased	48	12
Chemistry		
Sodium decreased	56	2.6
Phosphate decreased[2]	56	N/A
Aspartate aminotransferase increased	48	4.6
Alanine aminotransferase increased	45	5.3
Potassium decreased	34	5.3
Magnesium decreased	31	0
Creatinine increased	24	3.3
Potassium increased	21	1.3

* Laboratory abnormalities were graded based on CTCAE Version 5.0
[1] The denominator used to calculate the rate varied from 146 to 153 based on the number of patients with a baseline value and at least one post-treatment value.
[2] CTCAE Version 5.0 does not include numeric thresholds for grading of hypophosphatemia; all grades represent patients with lab value < Lower Limit of Normal (LLN).

Relapsed or Refractory Follicular Lymphoma (FL)

EPCORE FL-1

The safety of EPKINLY in combination with lenalidomide and rituximab was evaluated in EPCORE FL-1, an open-label, randomized, multicenter trial that included patients with relapsed or refractory FL after at least one line of systemic therapy *[see Clinical Studies (14.2)]*. The study excluded patients with transformed lymphoma, absolute neutrophil count < 1.0 x 10^9/L, platelet count < 70 x 10^9/L (or < 50 x 10^9/L if bone marrow infiltration by lymphoma or splenomegaly), known active infection, creatinine clearance < 50 mL/min, alanine or aspartate transaminase > 3 times the upper limit of normal, and clinically significant cardiovascular disease. Patients were randomized to receive EPKINLY in combination with lenalidomide and rituximab (N=243) or lenalidomide and rituximab alone (N=238). Patients received EPKINLY via subcutaneous injection in 28-day cycles for a total of 12 cycles or until disease progression or unacceptable toxicity, whichever occurred first. Of the 243 patients who received EPKINLY, 131 received the recommended 3 step-up dosage schedule.

The recommended EPKINLY dosage schedule was:

- Cycle 1: EPKINLY 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: EPKINLY 48 mg on Days 1, 8, 15, and 22
- Cycles 4-12: EPKINLY 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. 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.

Safety results are based on all 243 patients who received EPKINLY, with the exception of data for CRS and ICANS which are based on patients who received EPKINLY at the recommended dosage schedule. The median duration of exposure in this arm was 10 cycles for EPKINLY and 9 cycles for lenalidomide.

Serious adverse reactions occurred in 51% of these patients, including serious infections in 28% of patients and serious CRS in 12% of patients. Fatal adverse reactions within 60 days of last treatment occurred in 0.8% of patients.

Adverse reactions led to permanent discontinuation of EPKINLY in 6% of patients and dose interruption in 75% of patients, with infection as a leading cause. Adverse reactions leading to interruption of EPKINLY in ≥ 5% of patients included respiratory tract infections, CRS, and rash.

In the EPKINLY arm, adverse reactions led to lenalidomide dose interruption in 72%, dose reduction in 22%, and permanent discontinuation in 15%.

The most common (≥ 20%) adverse reactions in the EPKINLY arm were rash, upper respiratory tract infections, fatigue, injection site reactions, constipation, diarrhea, CRS, pneumonia, COVID-19, and fever. The most common Grade 3 to 4 laboratory abnormalities (≥ 10%) were decreases in neutrophil count, lymphocyte count, and platelets.

Table 13 summarizes select adverse reactions in EPCORE FL-1.

Table 13: Adverse Reactions (≥ 10% All Grade and ≥ 5% Higher) in Patients with Relapsed or Refractory FL Who Received EPKINLY in Combination with Lenalidomide and Rituximab in EPCORE FL-1

Adverse Reaction[§]	EPKINLY + Lenalidomide and Rituximab		Lenalidomide and Rituximab	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
	(N=131)		(N=238)	
Immune system disorders				
Cytokine release syndrome	24[†*]	0	0.8	0
	(N=243)		(N=238)	
Skin and subcutaneous tissue disorders				
Rash[a]	46	11[#]	34	6[#]
Infections and infestations				
Upper respiratory tract infections[b]	33	3.3	18	0.4[#]

Adverse Reaction[§]	EPKINLY + Lenalidomide and Rituximab		Lenalidomide and Rituximab	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Pneumonia[c]	24	16[#]	8[††]	4.6
COVID-19[d]	23	5[#]	13	1.3[#]
General disorders and administration site conditions				
Fatigue[e]	31	4.9[#]	24	2.1[#]
Injection site reactions	27	0	0.4	0
Fever	23	0.4[#]	11	1.3[#]
Gastrointestinal disorders				
Constipation	26	0.8[#]	21	0
Mucositis[f]	12	0	3.4	0
Nervous system disorders				
Neurological changes[g]	15	1.2[#]	8	1.3[#]
Headache	11	0	3.8	0
Psychiatric disorders				
Insomnia	14	0	2.9	0

This table includes a combination of grouped and ungrouped terms.
[§] Adverse reactions were graded using CTCAE Version 5.0. CRS was graded using ASTCT consensus criteria (Lee et al., 2019).
[†] The frequency of CRS is based on 131 patients who received EPKINLY at the recommended dosage schedule *[see Dosage and Administration (2.2)]*. Grade 1 CRS: 19%; Grade 2 CRS: 5%.
[*] The frequency of CRS among the 243 patients who received either the 2-step up or 3-step up dosage schedule was the following: Any grade CRS 35%; Grade 1 CRS: 28%; Grade 2 CRS: 7%.
[#] Only Grade 3 adverse reactions occurred.
[††] Includes one case with a fatal outcome.
[a] Rash includes blister, dermatitis, erythema, rash, skin exfoliation, skin reaction, toxic skin eruption, urticaria and related terms.
[b] Upper respiratory tract infections include sinusitis, laryngitis, nasopharyngitis, pharyngitis, rhinitis, rhinovirus infection, upper respiratory tract infection, and related terms.
[c] Pneumonia includes pneumonia, COVID-19 pneumonia, pneumonia fungal, Pneumocystis jirovecii pneumonia, pneumonia cytomegaloviral, and related terms.
[d] COVID-19 includes COVID-19, COVID-19 pneumonia, coronavirus infection, coronavirus pneumonia.
[e] Fatigue includes asthenia, fatigue, lethargy, malaise.
[f] Mucositis includes gingival pain, glossitis, mouth ulceration, mucosal infection, mucosal inflammation, oral discomfort, oral mucosal exfoliation, oropharyngeal pain, stomatitis.
[g] Neurological changes include brain fog, cognitive disorder, confusional state, disturbance in attention, dysphonia, epilepsy, essential tremor, gait disturbance, hypoacusis, lethargy, loss of consciousness, memory impairment, somnolence, syncope, tremor, vertigo, and ICANS.

Other clinically relevant adverse reactions include:
Gastrointestinal disorders: diarrhea (26%), nausea (16%), abdominal pain (11%), vomiting (4.1%)
Musculoskeletal and connective tissue disorders: musculoskeletal pain (14%), arthralgia (8%)
Nervous system disorders: peripheral neuropathy (12%), dizziness (7%), ICANS (0.8%)
General disorders: edema (12%)
Infections: cytomegalovirus infection (7%), herpesvirus infection (7%), sepsis (2.9%)
Blood and lymphatic system disorders: febrile neutropenia (6%)

Neoplasms: tumor flare (1.2%)

Table 14 summarizes laboratory abnormalities in EPCORE FL-1. Grade 4 laboratory abnormalities in ≥ 2% of the EPKINLY arm included decreases in neutrophils (41%), lymphocytes (13%), and platelets decreased (4.1%).

Table 14: Select Laboratory Abnormalities (≥ 30% All Grade and ≥ 10% Higher) That Worsened from Baseline in Patients with Relapsed or Refractory FL Who Received EPKINLY in Combination with Lenalidomide and Rituximab in EPCORE FL-1

Laboratory Abnormality	EPKINLY + Lenalidomide and Rituximab[1]		Lenalidomide and Rituximab[1]	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Neutrophils decreased	86	67	75	41
Lymphocytes decreased	86	62	56	15
Hemoglobin decreased	66	7	52	4.7
Platelets decreased	50	10	37	7
Chemistry				
Alanine aminotransferase increased	58	7	36	0.9
Phosphate decreased[2]	49	N/A	28	N/A
Sodium decreased	43	4.1	23	2.6
Potassium decreased	41	9	20	4.7
Aspartate aminotransferase increased	40	2.9	29	0.9

Laboratory abnormalities were graded based on CTCAE Version 5.0
[1] The denominator used to calculate the rate varied from 240 to 242 in the EPKINLY arm, and 225 to 236 in the comparator arm, based on the number of patients with a baseline value and at least one post-treatment value.
[2] CTCAE Version 5.0 does not include numeric thresholds for grading of hypophosphatemia; all grades represent patients with lab value < Lower Limit of Normal (LLN).

EPCORE NHL-1

The safety of EPKINLY as monotherapy was evaluated in EPCORE NHL-1, a single-arm study of patients with relapsed or refractory FL after two or more lines of systemic therapy who received EPKINLY following a 2-step up dosage schedule (N=127) *[see Clinical Studies (14.2)]*. A separate dose optimization cohort evaluated the recommended 3-step up dosage schedule for CRS mitigation (N=86), where EPKINLY was administered via subcutaneous injection until disease progression or unacceptable toxicities according to the following 28-day cycle schedule:

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

With the exception of CRS, the safety results presented below and in Tables 15 and 16 represent data from patients who received the 2-step up dosage schedule. The data presented for CRS reflects the 86 patients who received the recommended 3-step up dosage schedule. 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%.

Recommended 3-step up Dosage Schedule
Of the 86 patients with relapsed or refractory FL who received EPKINLY following the recommended 3-step up dosage schedule, the median age was 63 years (range: 33 to 90), 57% were male, and 100% had an ECOG performance status of 0 or 1.

The median duration of exposure was 5 cycles (range: 1 to 12 cycles). CRS occurred in 49% of patients, with Grade 1 CRS occurring in 45% and Grade 2 in 9% of patients. Serious adverse reactions due to CRS occurred in 28% of patients who received EPKINLY. Dose interruptions due to CRS occurred in 19% of patients who received EPKINLY.

2-step up Dosage Schedule
Of the 127 patients with relapsed or refractory FL who received EPKINLY following a 2-step up dosage schedule, the median age was 65 years (range: 39 to 84), 62% were male, and 95% had an ECOG performance status of 0 or 1 *[see Clinical Studies (14.2)]*. The median duration of exposure for patients receiving EPKINLY was 8 cycles (range: 1 to 33 cycles).

Serious adverse reactions occurred in 66% of patients who received EPKINLY. Serious adverse reactions in ≥ 5% of patients included CRS, COVID-19, pneumonia, and second primary malignancies.

Fatal adverse reactions occurred in 9% of patients who received EPKINLY, including COVID-19 (5%), pneumonitis (1.6%), cardiac failure (0.8%), pneumonia (0.8%), and sepsis (0.8%).

Permanent discontinuation of EPKINLY due to an adverse reaction occurred in 19% of patients who received EPKINLY. Adverse reactions which resulted in permanent discontinuation of EPKINLY in ≥ 2% of patients included COVID-19, Hepatitis E, pneumonitis, and second primary malignancy.

Dosage interruptions of EPKINLY due to an adverse reaction occurred in 59% of patients who received EPKINLY. Adverse reactions which required dosage interruption in ≥ 5% of patients included COVID-19, CRS, pneumonia, upper respiratory tract infection, and fatigue.

The most common (≥ 20%) adverse reactions were injection site reactions, CRS, COVID-19, fatigue, upper respiratory tract infection, musculoskeletal pain, rash, diarrhea, pyrexia, cough, and headache. The most common Grade 3 to 4 laboratory abnormalities (≥ 10%) were decreased lymphocyte count, decreased neutrophil count, decreased white blood cell count, and decreased hemoglobin.

Table 15 summarizes the adverse reactions in EPCORE NHL-1.

Table 15: Adverse Reactions (≥ 10%) in Patients with Relapsed or Refractory FL Who Received EPKINLY as Monotherapy in EPCORE NHL-1

Adverse Reaction[§]	EPKINLY	
	All Grades (%)	Grade 3 or 4 (%)
(N=86)[†]		
Immune system disorders		
Cytokine release syndrome[‡*]	49	0
(N=127)		
General disorders and administration site conditions		
Injection site reactions[a]	58	0
Fatigue[a]	37	5[#]
Pyrexia[a]	26	2[#]
Edema[a]	17	0
Infections and Infestations		
COVID-19[b]	40	19
Upper respiratory tract infection[c]	29	2[#]
Pneumonia[d]	17	13[#]
Urinary tract infection[a]	13	5[#]
Herpesvirus infection[e]	12	1.6[#]
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[a]	28	0.8[#]
Arthralgia	14	0.8[#]
Skin and subcutaneous disorders		
Rash[a]	28	0
Gastrointestinal disorders		
Diarrhea	26	1.6[#]
Nausea	17	0
Abdominal pain[a]	17	0.8[#]
Constipation	16	0
Mucositis[f]	12	0
Respiratory disorders		
Cough[a]	20	0
Dyspnea[a]	17	0
Nervous system disorders		
Headache	20	0
Neurological changes[g]	13	0
Peripheral neuropathy and paresthesia[h]	13	1.6[#]
Dizziness	11	0
Psychiatric disorders		
Insomnia	13	0
Renal and urinary disorders		

Renal insufficiency[i]	10	1.6[#]

[§] Adverse reactions were graded based on CTCAE Version 5.0.
[†] The frequency of CRS is based on 86 patients with FL who received the recommended 3-step up dosage schedule in EPCORE NHL-1 *[see Dosage and Administration (2.2)]*.
[‡] CRS was graded using ASTCT consensus criteria (Lee et al., 2019).
[*] The frequency of CRS based on the 127 patients with FL who received the 2-step up dosage schedule in EPCORE NHL-1 was the following: Any grade CRS 66%; Grade 1 CRS: 50%; Grade 2 CRS: 26%; Grade 3 CRS: 1.6%.
[#] Only Grade 3 adverse reactions occurred.
[a] Includes related grouped terms.
[b] COVID-19 includes COVID-19, COVID-19 pneumonia, SARS-CoV-2 test positive.
[c] Upper respiratory tract infection includes preferred terms with upper respiratory infection and sinusitis, laryngitis viral, nasopharyngitis, oropharyngitis fungal, pharyngitis, rhinitis, rhinovirus infection, tonsillitis.
[d] Pneumonia includes preferred terms with pneumonia, bronchopulmonary aspergillosis, infectious pleural effusion, infective exacerbation of bronchiectasis, Pneumocystis jirovecii pneumonia, pneumonia respiratory syncytial viral.
[e] Herpesvirus infection includes herpes simplex, herpes simplex reactivation, herpes virus infection, herpes zoster, oral herpes, varicella zoster virus infection.
[f] Mucositis includes aphthous ulcer, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal pain, stomatitis, tongue ulceration.
[g] Neurological changes includes amnesia, aphasia, balance disorder, brain fog, confusional state, dysphonia, encephalopathy, extrapyramidal disorder, hallucination, hypoacusis, memory impairment, mental status changes, tremor, vertigo.
[h] Peripheral neuropathy and paresthesia includes bell's palsy, hypoesthesia, neuralgia, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, polyneuropathy.
[i] Renal insufficiency includes acute kidney injury, blood creatinine increased, renal impairment.

Clinically relevant adverse reactions in < 10% of patients (N=127) who received EPKINLY included vomiting, pruritus, hepatotoxicity, ICANS, lower respiratory tract infections, cardiac arrhythmias, respiratory tract infections, pneumonitis, second primary malignancy, vision changes, cellulitis, febrile neutropenia, cardiac failure, cytomegalovirus infection and sepsis.

Table 16 summarizes laboratory abnormalities in EPCORE NHL-1.

Table 16: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients with Relapsed or Refractory FL Who Received EPKINLY in EPCORE NHL-1

Laboratory Abnormality*	**EPKINLY[1] (N=127)**	
	All Grades	**Grade 3 or 4 (%)**
Hematology		
Lymphocytes decreased	94	82
Hemoglobin decreased	59	10
White blood cells decreased	58	19
Neutrophils decreased	55	30
Platelets decreased	49	8
Chemistry		
Sodium decreased	51	1.6
ALT increased	47	8
AST increased	44	6
Creatinine increased	36	0.8

Laboratory Abnormality*	EPKINLY[1] (N=127)	
	All Grades	Grade 3 or 4 (%)
Alkaline phosphatase increased	29	0
Bilirubin increased	28	1.6
Potassium decreased	20	3.1
Magnesium decreased	20	0.8

* Laboratory abnormalities were graded based on CTCAE Version 5.0
[1] The denominator used to calculate the rate varied from 123 to 127 based on the number of patients with a baseline value and at least one post-treatment value.

Other Clinical Trials Experience

The following adverse reactions have been reported following administration of epcoritamab-bysp: hypogammaglobulinemia.

6.2 Postmarketing Experience

The following adverse reaction has been identified during post-approval use of EPKINLY. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Immune system disorders*: Hemophagocytic Lymphohistiocytosis (HLH)

7 DRUG INTERACTIONS

For certain CYP substrates, minimal changes in the concentration may lead to serious adverse reactions. Monitor for toxicity or drug concentrations of such CYP substrates when co-administered with EPKINLY.

Epcoritamab-bysp causes release of cytokines *[see Clinical Pharmacology (12.2)]* that may suppress activity of CYP enzymes, resulting in increased exposure of CYP substrates. Increased exposure of CYP substrates is more likely to occur after the first dose of EPKINLY and up to 14 days after the first 48 mg dose, and during and after CRS *[see Warnings and Precautions (5.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on the mechanism of action, EPKINLY may cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on the use of EPKINLY in pregnant women to evaluate for a drug-associated risk. No animal reproductive or developmental toxicity studies have been conducted with epcoritamab-bysp.

Epcoritamab-bysp causes T-cell activation and cytokine release; immune activation may compromise pregnancy maintenance. In addition, based on expression of CD20 on B-cells and the finding of B-cell depletion in non-pregnant animals, epcoritamab-bysp can cause B-cell lymphocytopenia in infants exposed to epcoritamab-bysp in-utero. Human immunoglobulin G (IgG) is known to cross the placenta; therefore, EPKINLY has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to the fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary
There is no information regarding the presence of epcoritamab-bysp in human milk, the effect on the breastfed child, or milk production. Because maternal IgG is present in human milk, and there is potential for epcoritamab-bysp absorption leading to serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with EPKINLY and for 4 months after the last dose.

8.3 Females and Males of Reproductive Potential

EPKINLY may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing
Verify pregnancy status in females of reproductive potential prior to initiating EPKINLY.

Contraception
Females
Advise females of reproductive potential to use effective contraception during treatment with EPKINLY and for 4 months after the last dose.

8.4 Pediatric Use

The safety and efficacy of EPKINLY in pediatric patients have not been established.

8.5 Geriatric Use

LBCL
In patients with relapsed or refractory LBCL who received EPKINLY in EPCORE NHL-1, 77 (49%) were 65 years of age and older, and 29 (19%) were 75 years of age or older. No clinically

meaningful differences in safety or efficacy were observed between patients with relapsed or refractory LBCL who were 65 years of age and older compared with younger adult patients.

FL
In patients with relapsed or refractory FL who received EPKINLY in combination with lenalidomide and rituximab in EPCORE FL-1, 88 (36%) were 65 years of age or older and 20 (8%) were 75 years of age or older. No clinically meaningful differences in safety or efficacy were observed between patients who were 65 years of age and older compared with younger patients.

In patients with relapsed or refractory FL who received EPKINLY in EPCORE NHL-1, 66 (52%) were 65 years of age or older, and 16 (13%) were 75 years of age and older.

In patients with relapsed or refractory FL, there was a higher rate of fatal adverse reactions, primarily infections, including COVID-19, in patients older than 65 years of age compared to younger adult patients. No overall difference in efficacy was observed in patients with relapsed or refractory FL who were 65 years of age and older compared with younger patients.

11 DESCRIPTION

Epcoritamab-bysp is a bispecific CD20-directed CD3 T-cell engager; it is a humanized bispecific IgG1 antibody. Epcoritamab-bysp is manufactured in Chinese hamster ovary (CHO) cells using recombinant DNA technology and has an approximate molecular weight of 149 kDa.

EPKINLY (epcoritamab-bysp) injection for subcutaneous use is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution, free of visible particles.

Each single-dose 4 mg/0.8 mL vial contains epcoritamab-bysp (4 mg), acetic acid (0.19 mg), polysorbate 80 (0.32 mg), sodium acetate (1.7 mg), sorbitol (21.9 mg) and Water for Injection, USP. The pH is 5.5.

Each single-dose 48 mg/0.8 mL vial contains epcoritamab-bysp (48 mg), acetic acid (0.19 mg), polysorbate 80 (0.32 mg), sodium acetate (1.7 mg), sorbitol (21.9 mg) and Water for Injection, USP. The pH is 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Epcoritamab-bysp 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.

In vitro, epcoritamab-bysp activated T-cells, caused the release of proinflammatory cytokines, and induced lysis of B-cells.

In nonclinical studies, the combination of epcoritamab-bysp and rituximab resulted in both T-cell mediated cytotoxicity and natural killer (NK) cell mediated antibody-dependent cellular cytotoxicity (ADCC).

12.2 Pharmacodynamics

Circulating B-Cell Count

Circulating B-cells decreased to undetectable levels (< 10 cells/microliter) after administration of the approved recommended dosage of EPKINLY in patients who had detectable B-cells at treatment initiation by Cycle 1 Day 15 and the depletion was sustained while patients remained on treatment.

Cytokine Concentrations

Plasma concentrations of cytokines (IL-2, IL-6, IL-10, TNF-α, and IFN-γ) were measured. Transient elevation of circulating cytokines was observed at dose levels of 0.04 mg and above. After administration of the approved recommended dosages of EPKINLY, cytokine levels increased within 24 hours after the first dose on Cycle 1 Day 1, generally reached maximum levels after the first 48 mg dose, and returned to baseline prior to the second 48 mg full dose.

12.3 Pharmacokinetics

Pharmacokinetic (PK) parameters were evaluated at the approved recommended dosage (48 mg) and are presented as geometric mean (CV%) unless otherwise specified.

Epcoritamab-bysp area under the concentration-time curve (AUC) increased more than proportionally over a full dosage range from 1.5 to 60 mg (0.03125 to 1.25 times the approved recommended dosage).

Epcoritamab-bysp maximum concentration (10.2 mcg/mL [43.2%]) is achieved after the first dose of the Q2W regimen (i.e., the first dose of Cycle 4). No clinically significant differences in pharmacokinetic parameters were observed between patients with relapsed or refractory LBCL and patients with relapsed or refractory FL. PK exposures are summarized for the recommended dosage of EPKINLY in Table 17.

Table 17: Exposure Parameters of Epcoritamab-bysp in Subjects with Relapsed or Refractory LBCL or FL Following Recommended Dosage

	C_{avg} (mcg/mL)[1]	C_{max} (mcg/mL)[1]	C_{trough} (mcg/mL)[1]
First full 48 mg dose[2]	1.3 (113.3%)	1.7 (106.7%)	1.4 (100.9%)
End of weekly dosing (end of Cycle 3)	9.1 (45.9%)	9.9 (43.4%)	7.8 (52.4%)
End of every 2-week dosing (end of Cycle 9)	5.3 (57%)	6.7 (49.4%)	3.6 (81.5%)

Steady state[3] with every 4-week dosing	2.4 (73.3%)	4.2 (59.8%)	1.1 (134.1%)

[1] Values are geometric mean with geometric CV%.
[2] First full 48 mg dose is on the first day of Week 3 in subjects with relapsed or refractory LBCL and on the first day of Week 4 in subjects with relapsed or refractory FL.
[3] Steady state values are approximated at Cycle 15 (Week 60).

Absorption
The median (range) T_{max} of epcoritamab-bysp after the first full dose and end of the weekly dosing regimen (end of Cycle 3) treatment doses were 4 (0.3 to 7) days and 2.3 (0.3 to 3.2) days, respectively.

Distribution
The apparent total volume of distribution is 25.6 L (82%).

Elimination
The half-life of full dose epcoritamab-bysp (48 mg) was approximately 22 days (58%) at the end of Cycle 3, with apparent total clearance of approximately 0.53 L/day (40%) after the end of Cycle 3.

Metabolism
Epcoritamab-bysp is expected to be metabolized into small peptides by catabolic pathways.

Specific Populations
No clinically significant differences in the PK of epcoritamab-bysp were observed based on age (20 to 89 years), sex, race (White or Asian), mild to moderate renal impairment (creatinine clearance [CLcr] 30 to < 90 mL/min as estimated by Cockcroft-Gault formula), and mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1 to 1.5 times ULN and any AST) after accounting for differences in bodyweight.

The effects of severe renal impairment (CLcr 15 to < 30 mL/min), end-stage renal disease (CLcr < 15 mL/min), or moderate to severe hepatic impairment (total bilirubin > 1.5 times ULN and any AST) on the PK of epcoritamab-bysp are unknown.

Body Weight
In patients who received the recommended dosage of EPKINLY, geometric mean average concentration following the first full 48 mg dose was 31% lower in the higher body weight (BW) group (85 to 172 kg) and 13% higher in the lower BW group (39 to 65 kg) compared to patients with BW of 65 to less than 85 kg.

Drug Interaction Studies
No clinical studies evaluating the drug interaction potential of epcoritamab-bysp have been conducted.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies (ADA) in the study described below with the incidence of ADA in other studies, including those of epcoritamab-bysp.

Anti-epcoritamab-bysp antibodies developed in 2.6% of patients (4 of 156) with LBCL and 4.2% of patients (8 of 190) with FL treated with EPKINLY in EPCORE NHL-1 (up to 10 cycles) *[see Clinical Studies (14.1, 14.2)]* using an electrochemiluminescence immunoassay (ECLIA). Anti-epcoritamab-bysp antibodies developed in 2.1% of patients (5 of 236) with FL treated with EPKINLY in combination with lenalidomide and rituximab in EPCORE FL-1 (up to 12 cycles) *[see Clinical Studies (14.2)]* using an ECLIA. Because of the low occurrence of anti-drug antibodies, the effect of these antibodies on the PK, pharmacodynamics, safety, and effectiveness of epcoritamab-bysp is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with epcoritamab-bysp.

No dedicated studies have been conducted to evaluate the effects of epcoritamab-bysp on fertility.

14 CLINICAL STUDIES

14.1 DLBCL and High-grade B-cell Lymphoma

The efficacy of EPKINLY was evaluated in EPCORE NHL-1 (Study GCT3013-01; NCT03625037), an open-label, multi-cohort, multicenter, single-arm trial in 157 patients with relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy. The study excluded patients with CNS involvement of lymphoma, allogeneic HSCT or solid organ transplant, ongoing active infection, and any patients with known impaired T-cell immunity. Patients received EPKINLY monotherapy at the recommended 2-step up dosage schedule:

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

Patients continued to receive EPKINLY until disease progression or unacceptable toxicity. In the setting of a suspected tumor flare reaction, continued treatment was permitted.

The efficacy population includes 148 patients with DLBCL, not otherwise specified (NOS), including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma. Of the 148 patients, the median age was 65 years (range: 22 to 83), 62% were male, 97% had an ECOG performance status of 0 or 1, and 3% had an ECOG performance status of 2. Race was reported in 125 (84%) patients; of these patients, 61% were White, 20% were Asian, and 0.7% were Native Hawaiian or Other Pacific Islander. There were no Black or African American or Hispanic or Latino patients treated in the clinical trial as reported. The diagnosis was DLBCL NOS in 86%, including 27% with DLBCL transformed from indolent lymphoma, and high-grade B-cell lymphoma in 14%. The median number of prior therapies was 3 (range: 2 to 11), with 30% receiving 2 prior therapies, 30% receiving 3 prior therapies, and 40% receiving 4 or more prior therapies. Eighteen percent had prior autologous HSCT, and 39% had prior chimeric antigen receptor (CAR) T-cell therapy. Eighty-two percent of patients had disease refractory to last therapy and 29% of patients were refractory to CAR T-cell therapy.

Efficacy was established based on overall response rate (ORR) and duration of response as assessed by an Independent Review Committee (IRC) using Lugano 2014 criteria. The efficacy results are summarized in Table 18.

Table 18: Efficacy Results in EPCORE NHL-1 in Patients with DLBCL and High-grade B-cell Lymphoma

Endpoint[a]	**EPKINLY (N=148)**
ORR[b], n (%)	90 (61)
(95% CI)	(52.5, 68.7)
CR, n (%)	56 (38)
(95% CI)	(30.0, 46.2)
PR, n (%)	34 (23)
(95% CI)	(16.5, 30.6)
DOR	
Median (95% CI), months	15.6 (9.7, NR)
9-month estimate[c] (95% CI), %	63 (51.5, 72.4)

ORR = overall response rate; CI = confidence interval; CR = complete response; PR = partial response; DOR = duration of response; NR = not reached.
[a] Determined by Lugano criteria (2014) as assessed by independent review committee (IRC).
[b] Early response assessments were evaluated in the context of potential flare reactions. Of 90 patients who achieved an objective response, 9 patients had early flare reactions identified with objective response demonstrated on subsequent imaging per Lugano criteria.
[c] Kaplan-Meier estimate.

The median time to response was 1.4 months (range: 1 to 8.4 months). Among responders, the median follow-up for DOR was 9.8 months (range: 0.0 to 17.3 months).

14.2 Follicular Lymphoma

EPKINLY in Combination with Lenalidomide and Rituximab for FL
The efficacy of EPKINLY in combination with lenalidomide and rituximab was evaluated in EPCORE FL-1 (Study M20-638; NCT05409066), an open-label, randomized, multicenter, global trial in patients with relapsed or refractory FL after at least one line of systemic therapy. Patients were randomized to receive 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 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 EPKINLY dosage schedule was:
- Cycle 1: EPKINLY 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: EPKINLY 48 mg on Days 1, 8, 15, and 22
- Cycles 4-12: EPKINLY 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 White, 24% Asian, and 2% were Black; 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 was established based on progression free survival (PFS) and overall response rate (ORR) as assessed by Independent Review Committee (IRC) using Lugano 2014 criteria.

The efficacy results, based on a prespecified interim analysis, are summarized in Table 19 and the Kaplan-Meier plot of PFS presented in Figure 1. The results are based on a median duration of follow-up of 10.4 months in the intention-to-treat population.

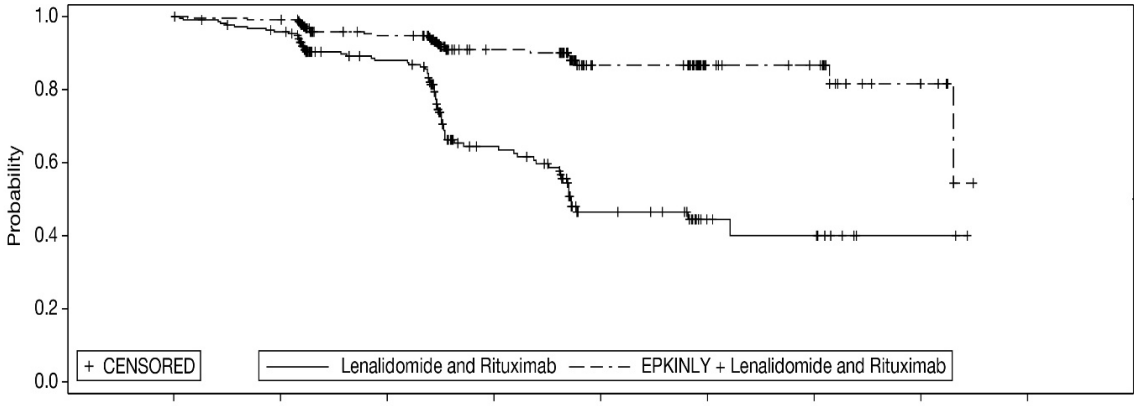
Table 19: Efficacy Results in EPCORE FL-1 in Patients with FL

Outcome per IRC	**EPKINLY + Lenalidomide and Rituximab (N=243)**	**Lenalidomide and Rituximab (N=245)**
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	
ORR, n (%)	216 (89)	181 (74)
(95% CI)	(84, 93)	(68, 79)
P-value[c,d]	< 0.0001	
CR, n (%)	181 (74)	106 (43)
(95% CI)	(69, 80)	(37, 50)
P-value[d]	< 0.0001	

PFS = progression free survival; CI = confidence interval; NR = not reached; ORR = overall response rate; CR = complete response.
[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.

Figure 1: Kaplan-Meier Plot of PFS per IRC



N of subjects at risk									
Lenalidomide and Rituximab	245	203	149	68	28	11	9	2	0
EPKINLY + Lenalidomide and Rituximab	243	224	182	103	57	29	24	8	0

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 EPKINLY arm and 25 (10%) deaths in the lenalidomide and rituximab arm.

EPKINLY as Monotherapy for FL
The efficacy of EPKINLY as monotherapy was evaluated in EPCORE NHL-1 (Study GCT3013-01; NCT03625037), an open-label, multi-cohort, multicenter, single-arm trial that

included patients with relapsed or refractory follicular lymphoma (FL) 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 EPKINLY monotherapy following a 2-step up dosage schedule:

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

Patients continued to receive 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 White, 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 was established based on overall response rate (ORR) determined by Lugano 2014 criteria as assessed by Independent Review Committee (IRC) and duration of response. The median follow-up for DOR was 14.8 months. The efficacy results are summarized in Table 20.

Table 20: Efficacy Results in EPCORE NHL-1 in Patients with FL

Endpoint[a]	**EPKINLY (N=127)**
ORR, n (%)	104 (82)
(95% CI)	(74.1, 88.2)
CR, n (%)	76 (60)
(95% CI)	(50.8, 68.4)
PR, n (%)	28 (22)
(95% CI)	(15.2, 30.3)
DOR	
Median (95% CI), months	NR (13.7, NR)
12-month estimate[b] % (95% CI)	68.4 (57.6, 77.0)

ORR = overall response rate; CI = confidence interval; CR = complete response; PR = partial response; DOR = duration of response; NR = not reached.
[a] Determined by Lugano criteria (2014) as assessed by independent review committee (IRC).
[b] Kaplan-Meier estimate.

The median time to first response was 1.4 months (range: 1 to 3 months).

In a separate dose optimization cohort in EPCORE NHL-1, 86 patients received the recommended 3-step up dosage schedule in Cycle 1 *[see Adverse Reactions (6.1)]*. The efficacy results in this cohort were comparable to the primary efficacy population.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied
EPKINLY (epcoritamab-bysp) 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:

Carton contents	NDC number
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

The vial stopper is not made with natural rubber latex.

Storage and Handling
Store refrigerated at 2°C to 8°C (36°F to 46°F). Keep in the original carton to protect from light. Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Cytokine Release Syndrome (CRS)
Inform patients of the risk of CRS, and to immediately contact their healthcare provider should signs and symptoms associated with CRS (e.g., pyrexia, hypotension, hypoxia, chills, tachycardia, headache, and dyspnea) occur at any time. Advise patients with DLBCL or high-grade B-cell lymphoma that they may be hospitalized after administration of the Cycle 1 Day 15 dosage of 48 mg and patients with FL after administration of the Cycle 1 Day 22 dosage of 48 mg. Patients who receive Cycle 1 Day 15 and patients who receive Cycle 1 Day 22 first full dosage of 48 mg at an outpatient facility should remain in proximity of a healthcare facility that can assess and manage CRS afterwards. Advise all patients who experience symptoms that

impair consciousness not to drive and refrain from operating heavy or potentially dangerous machinery until events resolve *[see Warnings and Precautions (5.1)]*.

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)
Advise patients of the risk of ICANS, to immediately contact their healthcare provider for signs and symptoms associated with ICANS, which may manifest, for example, as confusional state, lethargy, tremor, dysgraphia, aphasia, and non-convulsive status epilepticus, and that the onset of events may be delayed. Advise patients who experience symptoms of ICANS that impair consciousness to refrain from driving or operating heavy or potentially dangerous machinery until symptoms of ICANS resolve *[see Warnings and Precautions (5.2)]*.

Infections
Advise patients of the risk of serious infections, and to contact their healthcare professional for signs or symptoms of serious infection *[see Warnings and Precautions (5.3)]*.

Cytopenias
Discuss the signs and symptoms associated with cytopenias, including neutropenia and febrile neutropenia, anemia, and thrombocytopenia *[see Warnings and Precautions (5.4)]*.

Embryo-Fetal Toxicity
Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider if they are pregnant or become pregnant *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with EPKINLY and for 4 months after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation
Advise women not to breastfeed during treatment with EPKINLY and for 4 months after the last dose *[see Use in Specific Populations (8.2)]*.

Manufactured by:
Genmab US, Inc.
Plainsboro, NJ 08536, USA
1-855-4GENMAB (1-855-443-6622)
U.S. License Number: 2293

Marketed by:
Genmab US, Inc.
Plainsboro, NJ 08536
and
AbbVie Inc.
North Chicago, IL 60064

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MEDICATION GUIDE
EPKINLY® (ep-KIN-lee)
(epcoritamab-bysp)
injection, for subcutaneous use

What is the most important information I should know about EPKINLY?

EPKINLY can cause serious side effects, including:

- **Cytokine Release Syndrome (CRS)**. CRS is common during treatment with EPKINLY and can also be serious or lead to death. Tell your healthcare provider or get medical help right away if you develop any signs or symptoms of CRS, including:
  - fever of 100.4°F (38°C) or higher
  - dizziness or light-headedness
  - trouble breathing
  - chills
  - fast heartbeat
  - feeling anxious
  - headache
  - confusion
  - shaking (tremors)
  - problems with balance and movement, such as trouble walking

  Due to the risk of CRS, you will receive EPKINLY on a "step-up dosing schedule".
  - The step-up dosing schedule is when you receive 2 or 3 smaller "step-up" doses of EPKINLY during your first cycle of treatment (Cycle 1).
  - You will receive your first full dose of EPKINLY a week after your last step-up dose (this will be Day 15 or Day 22 of Cycle 1).
  - If your dose of EPKINLY is delayed for any reason, you may need to repeat the "step-up dosing schedule".
  - Before each dose in Cycle 1, you will receive medicines to help reduce your risk of CRS. You will also receive medicine for 3 days after each dose in Cycle 1. Your healthcare provider will decide if you need to receive medicine to help reduce your risk of CRS with future cycles.
  - See **"How will I receive EPKINLY?"** for more information about how you will receive EPKINLY.
- **Neurologic problems.** EPKINLY can cause serious neurologic problems that can be life-threatening and lead to death. Neurologic problems may happen days or weeks after you receive EPKINLY. Your healthcare provider may refer you to a healthcare provider who specializes in neurologic problems. Tell your healthcare provider right away if you develop any signs or symptoms of neurologic problems, including:
  - trouble speaking or writing
  - confusion and disorientation
  - drowsiness
  - tiredness or lack of energy
  - muscle weakness
  - shaking (tremors)
  - seizures
  - memory loss

Your healthcare provider will monitor you for signs and symptoms of CRS and neurologic problems during treatment with EPKINLY, as well as other side effects and treat you if needed. Your healthcare provider may temporarily stop or completely stop your treatment with EPKINLY if you develop CRS, neurologic problems, or any other side effects that are severe.

People with diffuse large B-cell lymphoma (DLBCL) or high-grade B-cell lymphoma may be hospitalized after receiving their first full dose of EPKINLY on Day 15 of Cycle 1 due to the risk of CRS and neurologic problems.

People with follicular lymphoma (FL) may be hospitalized after receiving their first full dose of EPKINLY on Day 22 of Cycle 1 due to the risk of CRS and neurologic problems.

See **"What are the possible side effects of EPKINLY?"** for more information about side effects.

What is EPKINLY?

EPKINLY is a prescription medicine used to treat adults with:

- certain types of DLBCL or high-grade B-cell lymphoma that has come back (relapsed) or that did not respond (refractory), after 2 or more treatments.
- follicular lymphoma that has come back or that did not respond to previous treatment, together with lenalidomide and rituximab.
- follicular lymphoma that has come back or that did not respond after 2 or more treatments.

It is not known if EPKINLY is safe and effective in children.

Before receiving EPKINLY, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection.
- are pregnant or plan to become pregnant. EPKINLY may harm your unborn baby.
  Females who are able to become pregnant:
  - Your healthcare provider should do a pregnancy test before you start treatment with EPKINLY.
  - You should use effective birth control (contraception) during treatment and for 4 months after your last dose of EPKINLY.

- Tell your healthcare provider if you become pregnant or think that you may be pregnant during treatment with EPKINLY.
- are breastfeeding or plan to breastfeed. It is not known if EPKINLY passes into your breast milk. Do not breastfeed during treatment and for 4 months after your last dose of EPKINLY.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive EPKINLY?

- EPKINLY will be given to you by your healthcare provider as an injection under your skin (subcutaneous injection), usually in the lower part of your stomach-area (abdomen) or thigh.
- Your EPKINLY treatment schedule is divided into cycles that are usually 28 days (4 weeks) long.
- Your healthcare provider will decide how many treatment cycles you will receive and how often you will receive EPKINLY in each cycle.
- See **"What is the most important information I should know about EPKINLY?"** for more information about how you will receive EPKINLY.

What should I avoid while receiving EPKINLY?

Do not drive, operate heavy machinery, or do other dangerous activities if you develop dizziness, confusion, tremors, sleepiness, or any other symptoms that impair consciousness until your signs and symptoms go away. These may be signs and symptoms of CRS or neurologic problems.

See **"What is the most important information I should know about EPKINLY?"** for more information about signs and symptoms of CRS and neurologic problems.

What are the possible side effects of EPKINLY?

EPKINLY can cause serious side effects, including:

- See **"What is the most important information I should know about EPKINLY?"**
- **Infections.** EPKINLY can cause serious infections that may lead to death. Your healthcare provider will check you for signs and symptoms of infection before and during treatment with EPKINLY. Your healthcare provider should prescribe medicines before you start treatment to help prevent infection and treat you as needed if you develop an infection during treatment with EPKINLY. Tell your healthcare provider right away if you develop any signs or symptoms of infection during treatment with EPKINLY, including:
  - fever of 100.4°F (38°C) or higher
  - cough
  - chest pain
  - tiredness
  - shortness of breath
  - painful rash
  - sore throat
  - pain during urination
  - feeling weak or generally unwell
  - confusion
- **Low blood cell counts.** EPKINLY can cause low blood cell counts which can be serious or severe. Your healthcare provider will check your blood cell counts during treatment with EPKINLY. EPKINLY may cause the following low blood cell counts:
  - **low white blood cell counts (neutropenia and lymphopenia).** Low white blood cells can increase your risk for infection.
  - **low red blood cell counts (anemia).** Low red blood cells can cause tiredness and shortness of breath.
  - **low platelet counts (thrombocytopenia).** Low platelet counts can cause bruising or bleeding problems.

Your healthcare provider may temporarily stop or completely stop treatment with EPKINLY if you develop certain side effects.

The most common side effects of EPKINLY when used alone in DLBCL or high-grade B-cell lymphoma or FL include:

- CRS
- injection site reactions
- tiredness
- muscle and bone pain
- fever
- diarrhea
- COVID-19
- rash
- stomach area (abdominal pain)

The most common severe abnormal laboratory test results with EPKINLY when used alone in DLBCL or high-grade B-cell lymphoma or FL include: decreased white blood cells, decreased red blood cells, and decreased platelets.

The most common side effects of EPKINLY when used together with lenalidomide and rituximab in follicular lymphoma include:

- rash
- upper respiratory tract infections
- tiredness
- injection site reactions
- constipation
- diarrhea
- CRS
- pneumonia
- COVID-19
- fever

The most common severe abnormal laboratory test results with EPKINLY when used together with lenalidomide and rituximab in follicular lymphoma include: decreased white blood cells and decreased platelets.

These are not all of the possible side effects of EPKINLY.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about safe and effective use of EPKINLY.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about EPKINLY that is written for health professionals.

What are the ingredients in EPKINLY?

Active ingredient: epcoritamab-bysp
Inactive ingredients: acetic acid, polysorbate 80, sodium acetate, sorbitol and Water for Injection.

Manufactured by: Genmab US, Inc., Plainsboro, NJ 08536
U.S. License Number: 2293
Marketed by: Genmab US, Inc., Plainsboro, NJ 08536 and AbbVie Inc., North Chicago, IL 60064

For more information, go to www.EPKINLY.com or call 1-855-4GENMAB (1-855-443-6622)

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: June 2026