PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrEPKINLY™

epcoritamab for injection

Concentrate for solution for injection, subcutaneous injection

4 mg in 0.8 mL (5 mg/mL)

epcoritamab injection

Solution for injection, subcutaneous injection

48 mg in 0.8 mL (60 mg/mL)

Antineoplastic Agent, bispecific antibody

EPKINLY, indicated for:

- the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL transformed from indolent lymphoma, high grade B-cell lymphoma (HGBCL), primary mediastinal B-cell lymphoma (PMBCL) or follicular lymphoma Grade 3B (FLG3b) after two or more lines of systemic therapy and who have previously received or are unable to receive CAR-T cell therapy

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for EPKINLY please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html"

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Date of Initial Authorization:
OCT 13, 2023

Submission Control Number: 271331

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

RECENT MAJOR LABEL CHANGES

Not applicable	

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

EPKINLY (epcoritamab injection / epcoritamab for injection) is indicated for:

- the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, DLBCL transformed from indolent lymphoma, high grade B-cell lymphoma (HGBCL), primary mediastinal B-cell lymphoma (PMBCL) or follicular lymphoma Grade 3B (FLG3b) after two or more lines of systemic therapy and who have previously received or are unable to receive CAR-T cell therapy.

1.1 Pediatrics

Pediatrics (< 18 years of age): EPKINLY is not indicated in the pediatric population, as the safety and efficacy of EPKINLY in pediatric patients less than 18 years of age have not been evaluated (see 4.2 Recommended Dose and Dosage Adjustment).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No clinically meaningful differences in safety or efficacy were observed between patients ≥ 65 years of age compared with younger adult patients (see 7 WARNINGS AND PRECAUTIONS, 7.1.4 Geriatrics; and 10.3 Pharmacokinetics, Special Populations and Conditions).

2 CONTRAINDICATIONS

EPKINLY is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Cytokine Release Syndrome (CRS)**, which may be serious or life-threatening occurred in patients receiving EPKINLY. Initiate treatment with EPKINLY step-up dosing schedule to reduce the risk of CRS. Withhold EPKINLY until CRS resolves, provide supportive care and treatment as needed, or permanently discontinue based on severity (see 7 WARNINGS AND PRECAUTIONS).

- **Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)**, which include life-threatening and fatal events have occurred in patients receiving EPKINLY. ICANS can be concurrent with CRS, occur following resolution of CRS, or occur in the absence of CRS. Withhold EPKINLY until ICANS resolves or permanently discontinue based on severity (see 7 WARNINGS AND PRECAUTIONS).

Patients should be monitored for 24 hours after the first full dose of EPKINLY for signs and symptoms of CRS and ICANS.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- EPKINLY should only be administered under the supervision of a health professional experienced in the treatment of cancer patients and who has access to appropriate medical support to manage severe reactions such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

- EPKINLY should not be administered to patients with active infections.

- EPKINLY should not be administered to patients who have recently (within 4 weeks) received a live or live-attenuated vaccine (see 7 WARNINGS AND PRECAUTIONS).

Premedication and Prophylaxis

- Consider initiating prophylaxis against *Pneumocystis jirovecii pneumonia* (PJP) and herpes virus infections prior to starting treatment with EPKINLY.
- EPKINLY should be administered to adequately hydrated patients. Details on recommended premedication for CRS is detailed in **Table 1**.

Table 1. Epcoritamab Premedication for CRS

Cycle	Patient requiring premedication	Premedication	Administration
Cycle 1	All patients	• Prednisolone (100 mg oral or IV) 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 IV) or equivalent • Acetaminophen (650 to 1000 mg oral)	• 30-120 minutes prior to the administration of EPKINLY
Cycle 2 and beyond	Patients who experienced Grade 2 or 3[a] CRS with previous dose	• Prednisolone (100 mg oral or IV) or equivalent	• 30-120 minutes prior to next administration of EPKINLY after a grade 2 or 3[a] 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. Patients will be permanently discontinued from EPKINLY after a Grade 4 CRS event.

Monitoring

Monitor patients for potential CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) following EPKINLY administrations during Cycle 1 and in subsequent cycles as needed at the discretion of the health professional. For 24 hours following administration of the first full dose of 48 mg (Day 15 of Cycle 1), patients should remain within proximity of a healthcare facility and be monitored for signs and symptoms of CRS and ICANS, or alternatively consider hospitalization. Counsel patients on the signs and symptoms associated with CRS and ICANS and on seeking immediate medical attention should signs or symptoms occur at any time (see 7 WARNINGS AND PRECAUTIONS).

4.2 Recommended Dose and Dosage Adjustment

- EPKINLY is administered by subcutaneous (SC) injection only.
- Patients receive a priming dose on Day 1 (0.16 mg) and an intermediate dose on Day 8 (0.8 mg) of Cycle 1 using the 4 mg/0.8 mL (5 mg/mL) EPKINLY vial with light blue cap that **requires dilution** before administration (see 4.3 Reconstitution and 4.4 Administration).
- The first **full** EPKINLY dose (48 mg) is taken on Day 15 of Cycle 1 using the 48 mg/0.8 mL (60 mg/mL) EPKINLY vial with orange cap that **is not** diluted (see 4.3 Reconstitution and 4.4 Administration).
- Weekly 48 mg doses of EPKINLY continue for Cycles 2 and 3 using the EPKINLY vial with the orange cap.
- Starting in Cycle 4 and continuing thru Cycle 9, the 48 mg EPKINLY doses are administered once every two weeks (Days 1 and 15 only of each cycle).
- Starting in Cycle 10, the 48 mg EPKINLY dose is taken once every 4 weeks (Day 1 only of each 28-day cycle).
- EPKINLY is taken according to the following schedule until disease progression or unacceptable toxicity.

Table 2. Dosing Schedule

	Cycle 1				Cycle 2 & 3				Cycle 4-9		Cycles 10+
Day of Cycle	1	8	15	22	1	8	15	22	1	15	1
EPKINLY Dose (mg)[a]	0.16	0.8	48	48	48	48	48	48	48	48	48
a. 0.16 mg is a priming dose, 0.8mg is an intermediate dose and 48 mg is a full dose.											

Table 3. Recommended Dose Modifications for Adverse Reactions

Adverse Reaction	Severity	Action
CRS (see 7 WARNINGS AND PRECAUTIONS)	Grades 1-3	• Withhold EPKINLY until resolution of CRS event. • Refer to 4.5 Missed Dose for how to properly resume treatment.
	Grade 4	• Permanently discontinue EPKINLY.

Adverse Reaction	Severity	Action
ICANS (see 7 WARNINGS AND PRECAUTIONS)	Grades 1-2	• Withhold EPKINLY until resolution of ICANS event. • Refer to 4.5 Missed Dose for how to properly resume treatment.
	Grade 3	• First episode: withhold EPKINLY until full resolution of event. • Refer to 4.5 Missed Dose for how to properly resume treatment. • Second episode: permanently discontinue EPKINLY.
	Grade 4	• Permanently discontinue EPKINLY.
Infections[1] (see 7 WARNINGS AND PRECAUTIONS)	Grades 1-3	• Withhold EPKINLY in patients with active infection, until the infection fully resolves. • Refer to 4.5 Missed Dose for how to properly resume treatment.
	Grade 4	• Consider permanent discontinuation of EPKINLY. • If EPKINLY is resumed following full resolution of symptoms, refer to 4.5 Missed Dose for how to properly resume treatment.
Neutropenia or febrile neutropenia[1] (see 8 ADVERSE REACTIONS)	Absolute neutrophil count less than 0.5×10^9/L	• Withhold EPKINLY until absolute neutrophil count is 0.5×10^9/L or higher. • Refer to 4.5 Missed Dose for how to properly resume treatment.
Thrombocytopenia[1] (see 8 ADVERSE REACTIONS)	Platelet count less than 50×10^9/L	• Withhold EPKINLY until platelet count is 50×10^9/L or higher. • Refer to 4.5 Missed Dose for how to properly resume treatment.
Other adverse reactions[1] (see 8 ADVERSE REACTIONS)	Grade 3 or higher	• Withhold EPKINLY until the toxicity resolves to Grade ≤ 1. • For events associated with severe outcomes, consider permanent discontinuation of therapy.
CRS and ICANS graded according to ASTCT consensus criteria. 1. Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0.		

Dosing in Special Populations

Pediatrics (< 18 years of age)

EPKINLY is not indicated in the pediatric population, as the safety and efficacy of EPKINLY in pediatric patients less than 18 years of age have not been evaluated.

Geriatric (≥ 65 years of age)

In the EPCORE NHL-1 study, 48 (31%) patients were ≥ 65 to < 75 years of age and 29 (18%) patients were ≥ 75 years of age. No clinically meaningful differences in safety or efficacy were observed between patients ≥ 65 years of age compared with younger adult patients.

Renal impairment

Dose adjustments are not considered necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment were excluded from clinical studies with EPKINLY and no dose recommendations can be made for these patients.

Hepatic impairment

Dose adjustments are not considered necessary in patients with mild hepatic impairment. Patients with moderate or severe hepatic impairment were excluded from clinical studies with EPKINLY and no dose recommendations can be made for these patients.

4.3 Reconstitution

Methods of Dose Preparation

To prepare EPKINLY priming (0.16 mg) and intermediate (0.8 mg) doses, EPKINLY must be diluted by a health professional using aseptic techniques.

The following table outlines the materials needed for preparation of the priming and intermediate doses.

Materials needed	
Priming Dose	**Intermediate Dose**
4 mg/0.8 mL (5 mg/mL) EPKINLY vial with **light blue** cap	4 mg/0.8 mL (5 mg/mL) EPKINLY vial with **light blue** cap
0.9% Sodium Chloride Injection, USP	0.9% Sodium Chloride Injection, USP
Two empty sterile vials between 10 and 20 mL	One empty sterile vial between 10 and 20 mL
Recommended Syringe Sizes: • Two 1 mL syringes • One 3 mL syringe • One 5 mL syringe • One 10 mL syringe	Recommended Syringe Sizes: • Two 1 mL syringes • One 5 mL syringe

Priming Dose (0.16 mg) Preparation Instructions – Two Separate Dilution Steps Required:

Use a new, appropriately sized, syringe and needle for each transfer step.

1) Prepare EPKINLY vial a) Retrieve one 4 mg/0.8 mL (5 mg/mL) EPKINLY (epcoritamab **for injection**) vial with the **light blue** cap 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) Use an empty vial of an appropriate size. Label this vial as **"dilution A"**. b) Using a 1 mL syringe, transfer **0.8 mL of EPKINLY** into vial labeled as **dilution A**. c) Using a 5 mL syringe, transfer **4.2 mL of 0.9% Sodium Chloride Injection, USP** into vial labeled as **dilution A**. d) Gently swirl the **dilution A** vial for 30 – 45 seconds. At end of first dilution for priming dose, the concentration is 0.8 mg/mL.
3) Perform second dilution a) Use the second empty vial that can hold 10 mL of solution. Label this vial as "**dilution B**". b) Using a 3 mL syringe, transfer **2.0 mL of solution** from the vial labeled as **dilution A** into the **dilution B** vial. The **dilution A** vial is no longer needed. c) Using a 10 mL syringe, transfer **8.0 mL of 0.9% Sodium Chloride Injection, USP** into the **dilution B** vial. d) Gently swirl the **dilution B** vial for 30 – 45 seconds. At end of second dilution for priming dose, the concentration is 0.16 mg/mL.
4) Withdraw dose a) Using a 1 mL syringe for SC injection, withdraw **1 mL of the solution** from the **dilution B** vial.
5) Label syringe Label the syringe 0.16 mg and include the time of day.

Discard the single-dose vial and any unused portions of EPKINLY in accordance with local requirements.

Use prepared EPKINLY immediately or store EPKINLY solution in a refrigerator and protect from light up to 24 hours from the time of preparation (see 11 STORAGE, STABILITY AND DISPOSAL).

Intermediate Dose (0.8 mg) Preparation Instructions – One dilution step required:

Use a new, appropriately sized, syringe and needle for each transfer step.

1) Prepare EPKINLY vial a) Retrieve one 4 mg/0.8 mL (5 mg/mL) EPKINLY (epcoritamab **for injection**) vial with the **light blue** cap 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) Use an empty vial of an appropriate size. Label this vial as **"dilution A"**. b) Transfer **0.8 mL of EPKINLY** into vial labeled as **dilution A**. c) Transfer **4.2 mL of 0.9% Sodium Chloride Injection, USP** into vial labeled as **dilution A**. d) Gently swirl the **dilution A** vial for 30 – 45 seconds. At end of dilution for intermediate dose, the concentration is 0.8 mg/mL.

3) Withdraw dose a) Using a 1 mL syringe for SC injection, withdraw **1 mL of the solution** from the **dilution A** vial.
4) Label syringe Label the syringe 0.8 mg and include the time of day.

Discard the single-dose vial and any unused portions of EPKINLY in accordance with local requirements.

Use prepared EPKINLY immediately or store EPKINLY solution in a refrigerator and protect from light up to 24 hours from the time of preparation (see 11 STORAGE, STABILITY AND DISPOSAL).

Full Dose (48 mg) Preparation Instructions:

DO NOT dilute. EPKINLY 48 mg/0.8 mL (60 mg/mL) vial is ready to use.

1) Prepare EPKINLY vial a) Retrieve one 48 mg/0.8 mL (60 mg/mL) EPKINLY (epcoritamab **injection**) vial with the **orange** cap 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 Withdraw **0.8 mL of the EPKINLY** into a syringe for subcutaneous injection.
3) Label syringe Label the syringe 48 mg and include the time of day.

Discard the single-dose vial and any unused portions of EPKINLY in accordance with local requirements.

4.4 Administration

EPKINLY should be administered by subcutaneous injection (SC) by a health professional.

The administration of EPKINLY takes place over the course of 28-day cycles, following the dosing schedule in 4.2 Recommended Dose and Dosage Adjustment, using priming (0.16 mg), intermediate (0.8 mg) and full (48 mg) doses.

Site of Administration

The injection site should be preferably in the lower part of the abdomen or the thigh. Changing the injection site from left or right side or vice versa is recommended especially during the weekly administration (Cycles 1-3).

4.5 Missed Dose

Table 4. Recommendations for Restarting Therapy with EPKINLY After Dosage Delay

Last Dose Administered	Time Since the Last Dose Administered	Action for Next Dose(s)[a]
0.16 mg on Cycle 1 Day 1	More than 8 days	Repeat 0.16 mg, then administer 0.8 mg the following week, followed by two weekly doses of 48 mg. Then resume the planned dosage schedule beginning with Day 1 of the subsequent cycle.
0.8 mg on Cycle 1 Day 8	14 days or less	Administer 48 mg then resume the recommended dosage schedule.
	More than 14 days	Repeat 0.16 mg, then administer 0.8 mg the following week, followed by two weekly doses of 48 mg. Then resume the planned dosage schedule beginning with Day 1 of the subsequent cycle.
48 mg on Cycle 1 Day 15 onwards	6 weeks or less	Administer 48 mg, then resume the recommended dosage schedule.
	More than 6 weeks	Repeat 0.16 mg, then administer 0.8 mg the following week, followed by two weekly doses of 48 mg. Then resume the planned dosage schedule beginning with Day 1 of the subsequent cycle.

a. Administer pretreatment medication prior to EPKINLY dose and monitor patients accordingly (see 4 DOSAGE AND ADMINISTRATION).

5 OVERDOSAGE

In the event of overdose, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate supportive treatment.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 5. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous	Concentrate for solution for injection/ 5 mg/mL 4 mg epcoritamab in 0.8 mL solution	Acetic acid, polysorbate 80, sodium acetate trihydrate, D-sorbitol, and water for injection
Subcutaneous	Solution for injection/ 60 mg/mL 48 mg epcoritamab in 0.8 mL solution	Acetic acid, polysorbate 80, sodium acetate trihydrate, D-sorbitol, and water for injection

EPKINLY concentrate for solution, for subcutaneous injection (4 mg [5 mg/mL]) and EPKINLY solution for subcutaneous injection (48 mg [60 mg/mL]) are sterile, preservative free, clear to slightly opalescent, colourless to slightly yellow solutions, practically free of visible particles, supplied in glass vials as:

- 4 mg per 0.8 mL (5 mg/mL) single dose vial, which must be diluted prior to use
- 48 mg per 0.8 mL (60 mg/mL) single dose vial

The vial stopper is not made with natural rubber latex.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Driving and Operating Machinery

EPKINLY may have an influence on the ability to drive or operate machinery. Patients experiencing symptoms that might affect their ability to drive or use machines (e.g., symptoms of CRS or ICANS, such as pyrexia, tachycardia, hypotension, chills, hypoxia, depressed level of consciousness) should be advised not to drive or use machines until symptoms resolve.

Endocrine and Metabolism

Tumour Lysis Syndrome

Tumour Lysis Syndrome (TLS) has been reported in patients receiving EPKINLY (see 8 ADVERSE REACTIONS). Patients at an increased risk for TLS are recommended to receive hydration and prophylactic treatment with a uric acid lowering agent. Patients should be monitored for signs or symptoms of TLS, especially patients with high tumour burden or rapidly proliferative tumours, and patients with reduced renal function. Patients should be monitored for blood chemistries and abnormalities should be managed promptly.

Hepatic /Biliary/Pancreatic

The safety and efficacy of EPKINLY in patients with moderate and severe hepatic impairment have not been studied (see 10.3 Pharmacokinetics, Special Populations and Conditions).

Immune

Cytokine Release Syndrome

Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving EPKINLY. The most common signs and symptoms of CRS include pyrexia, hypotension and hypoxia. Other signs and symptoms of CRS in greater than two patients include chills, tachycardia, headache and dyspnea.

The median time to onset of CRS from the most recent administered EPKINLY dose was 2 days (range: 1 to 11 days). The median time to onset after the first full dose was 20.6 hours (range: 0.2 to 7 days). Most CRS events occurred in Cycle 1 and were associated with the first full dose of EPKINLY. Median duration of CRS was 3 Days (range: 1 to 27 days). Administer prophylactic medications including corticosteroids to mitigate the risk of CRS (see 4 DOSAGE AND ADMINISTRATION). In addition to corticosteroids use, tocilizumab was used to manage CRS event in 15% of patients.

Monitor patients for CRS following EPKINLY administrations during Cycle 1 and in subsequent cycles as needed at the discretion of the health professional. For 24 hours following administration of the first full dose of 48 mg, patients should remain within proximity of a healthcare facility and be monitored for signs and symptoms of CRS, or alternatively consider hospitalization. At the first signs or symptoms of CRS, institute treatment of supportive care with tocilizumab and/or corticosteroids as per institutional guidelines considering the recommendations listed in **Table 6.** Counsel patients on the signs and symptoms associated with CRS and instruct patients to contact their health professional and seek immediate medical attention should signs or symptoms occur at any time.

Management of CRS may require either temporary delay or discontinuation of EPKINLY based on the severity of CRS as per recommendations in **Table 6**. Patients who experience CRS should be monitored more frequently during the next scheduled EPKINLY administration. Withhold or discontinue EPKINLY as indicated in **Table 3** (see 4 DOSAGE AND ADMINISTRATION).

Table 6. CRS Grading and Management in Clinical Trials with EPKINLY[a]

Grade	Recommended Therapy
Grade 1 • Fever (temperature ≥ 38°C) without hypotension or hypoxia	**Anticytokine Therapy:** Consider anticytokine therapy in certain cases (e.g., advanced age, high tumour burden, circulating tumour cells, fever refractory to antipyretics): Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg per dose). Repeat tocilizumab after at least 8 hours as needed. Maximum of 2 doses in a 24-hour period.

Grade	Recommended Therapy
	In case of concurrent ICANS choose alternative to tocilizumab (e.g., siltuximab, anakinra). See **Table 7.** **Corticosteroids:** Consider dexamethasone 10-20 mg per day (or equivalent). In case of concurrent ICANS, initiation of corticosteroids are highly recommended.
Grade 2[b] • Fever (temperature ≥ 38°C) **AND** • Hypotension not requiring vasopressors. **AND/OR** • Hypoxia requiring low-flow (≤ 6 L/minute) nasal cannula or blow-by	**Anticytokine Therapy** Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg per dose). Repeat tocilizumab after at least 8 hours as needed. Maximum of 2 doses in a 24-hour period. If CRS is refractory to initial anticytokine therapy, initiate/increase dose of corticosteroid therapy and consider alternative anticytokine therapy. In case of concurrent ICANS choose alternative to tocilizumab (e.g., siltuximab, anakinra). See **Table 7**. **Corticosteroids:** Consider dexamethasone 10-20 mg per day (or equivalent). In case of concurrent ICANS, initiation of corticosteroids is highly recommended.
Grade 3[b] • Fever (temperature ≥ 38°C) **AND** • Hypotension requiring 1 vasopressor with or without vasopressin. **AND/OR** • Hypoxia requiring high-flow (> 6 L/minute) nasal cannula, facemask, non-rebreather mask, or venturi mask	**Anticytokine therapy:** Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg per dose). Repeat tocilizumab after at least 8 hours as needed. Maximum of 2 doses in a 24-hour period. If CRS is refractory to initial anticytokine therapy, initiate/increase dose of corticosteroid therapy and consider alternative anticytokine therapy. In case of concurrent ICANS choose alternative to tocilizumab (e.g., siltuximab, anakinra). See **Table 7**. **Corticosteroids:** Dexamethasone (e.g., 10-20 mg IV every 6 hours). If no response, initiate methylprednisolone 1000 mg/day.

Grade	Recommended Therapy
Grade 4 • Fever (temperature ≥ 38°C) **AND** • Hypotension requiring ≥ 2 vasopressors (excluding vasopressin) **AND/OR** • Hypoxia requiring positive pressure ventilation (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	**Anticytokine Therapy:** Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg per dose). Repeat tocilizumab after at least 8 hours as needed. Maximum of 2 doses in a 24-hour period. If CRS is refractory to initial anticytokine therapy, initiate/increase dose of corticosteroid therapy and consider alternative anticytokine therapy. In case of concurrent ICANS choose alternative to tocilizumab (e.g., siltuximab, anakinra). See **Table 7**. **Corticosteroids:** Dexamethasone (e.g., 10-20 mg IV every 6 hours). If no response, initiate methylprednisolone 1000 mg/day.
CRS was graded according to ASTCT consensus criteria. **a. The recommendations describe the CRS management in Study EPCORE NHL-1. Treat CRS per institutional guidelines.** b. When Grade 2 or 3 CRS occurred with the second full dose or beyond, CRS prophylaxis was administered in clinical trials with each subsequent dose until EPKINLY was given without a subsequent CRS event (of any grade).	

Serious Infections

Treatment with EPKINLY increases the risk of infections. Serious infections, including fatal infections, infections with opportunistic pathogens and viral reactivation, were observed in patients treated with EPKINLY in clinical trials. The most frequent type of serious infections observed with EPKINLY were pneumonia, sepsis, COVID-19, COVID 19-pneumonia, cellulitis, bacteremia, septic shock, and upper respiratory tract infection.

Avoid administration of EPKINLY in patients with clinically significant active systemic infections. As appropriate, administer prophylactic antibiotics and consider surveillance testing for reactivation during treatment with EPKINLY (see 4 DOSAGE AND ADMINISTRATION). Monitor patients for signs and symptoms of infections and treat according to standard/local guidelines and practice.

Vaccines

Patients who received live vaccines were excluded from clinical studies with EPKINLY. Vaccination with live or live attenuated vaccines is not permitted for at least 4 weeks prior to the start of EPKINLY and at any point during treatment.

Neurologic

Immune effector cell associated neurotoxicity syndrome

Immune effector cell associated neurotoxicity syndrome (ICANS), including a fatal event, have occurred in patients receiving EPKINLY. ICANS, a serious or life-threatening neurologic event, may manifest as aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema.

The median time to onset of ICANS from the start of EPKINLY treatment (Cycle 1 Day 1) was 16.5 days (range: 8 to 141 days). The majority of cases of ICANS occurred within Cycle 1 of EPKINLY treatment, however some events occurred with delayed onset. The median duration of ICANS was 5 days (range: 1 to 9 days). The onset of ICANS can be concurrent with CRS, following resolution of CRS or in the absence of CRS.

Monitor patients for signs and symptoms of ICANS following EPKINLY administrations during Cycle 1 and in subsequent cycles as needed at the discretion of the health professional. For 24 hours following administration of the first full dose of 48 mg, patients should remain within proximity of a healthcare facility and be monitored for signs and symptoms of ICANS, or alternatively consider hospitalization. At the first signs or symptoms of ICANS start treatment with corticosteroids and non-sedating-anti-seizure medications as per institutional guidelines considering the recommendations in **Table 7**.

Counsel patients on the signs and symptoms of ICANS and that the onset of events may be delayed. Instruct patients to contact their health professional and seek immediate medical attention should signs or symptoms occur at any time. Delay or discontinue EPKINLY as recommended in **Table 3** (see 4 DOSAGE AND ADMINISTRATION).

Table 7. ICANS Grading and Management in Clinical Trials with EPKINLY[a]

Grade	Recommended Therapy
Grade 1	Dexamethasone, 10 mg IV every 12 hours Consider non-sedating anti-seizure medication (e.g., levetiracetam) until resolution of ICANS Anticytokine therapy *No concurrent CRS*: Anticytokine therapy not recommended. *Concurrent CRS*: Anticytokine therapy recommended. Choose alternative to tocilizumab (e.g., siltuximab, anakinra) if possible. • Consider anakinra as a daily dose of 100 mg SC or 200 mg SC (100 mg every 12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.
Grade 2	Dexamethasone at 10-20 mg IV every 12 hours

Grade	Recommended Therapy
	Consider non-sedating anti-seizure medication (e.g., levetiracetam) until resolution of ICANS. <u>Anticytokine therapy:</u> *No concurrent CRS:* Anticytokine therapy not recommended. *Concurrent CRS:* Anticytokine therapy recommended. Choose alternative to tocilizumab (e.g., siltuximab, anakinra) if possible. • Consider anakinra as a daily dose of 100 mg SC or 200 mg SC (100 mg every 12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.
Grade 3	Dexamethasone 10-20 mg IV every 6 hours. If no response, initiate methylprednisolone 1000 mg/day. Consider non-sedating anti-seizure medication (e.g., levetiracetam) until resolution of ICANS. <u>Anticytokine Therapy</u> *No concurrent CRS:* Anticytokine therapy not recommended. *Concurrent CRS:* Anticytokine therapy recommended: Choose alternative to tocilizumab (e.g., siltuximab, anakinra) if possible. • Consider anakinra as a daily dose of 100 mg SC or 200 mg SC (100 mg every 12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.
Grade 4	Dexamethasone 10-20 mg IV every 6 hours. If no response, initiate methylprednisolone 1000 mg/day. Consider non-sedating anti-seizure medication (e.g., levetiracetam) until resolution of ICANS. <u>Anticytokine therapy</u>: *No concurrent CRS:* Anticytokine therapy not recommended. *Concurrent CRS:* Anticytokine therapy recommended. Choose alternative to tocilizumab (e.g., siltuximab, anakinra) if possible.

Grade	Recommended Therapy
	• Consider anakinra as a daily dose of 100 mg SC or 200 mg SC (100 mg every 12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.
ICANS graded according to ASTCT ICANS Consensus Grading. a. The recommendations describe management of ICANS in Study EPCORE NHL-1. Treat ICANS per institutional guidelines.	

Renal

The safety and efficacy of EPKINLY in patients with severe renal impairment has not been studied (see 10.3 Pharmacokinetics, Special Populations and Conditions).

Reproductive Health: Female and Male Potential

- **Fertility**

  No fertility studies have been conducted with EPKINLY. The effects of epcoritamab on male and female fertility are not known.

7.1 Special Populations

7.1.1 Pregnant Women

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

Based on its mechanism of action, EPKINLY may cause fetal harm, including B-cell lymphocytopenia and alterations in normal immune responses, when administered to pregnant women, since IgG1 antibodies, such as epcoritamab, can cross the placental resulting in fetal exposure. There are no data on the use of EPKINLY in pregnant women. Developmental and reproduction animal studies have not been conducted with epcoritamab. Advise pregnant women of the potential risk to a fetus.

Women of childbearing potential should use effective contraception during treatment with EPKINLY and for at least 4 months after the last dose.

7.1.2 Breast-feeding

It is not known whether EPKINLY is excreted in human milk or its effect on milk production. Since IgGs are known to be present in milk, neonatal exposure to epcoritamab may occur via lactational transfer. Breast feeding should be discontinued during treatment with EPKINLY and for at least 4 months after the last dose.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): EPKINLY is not indicated in the pediatric population, as the safety and efficacy of EPKINLY in pediatric patients less than 18 years of age have not been evaluated.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): In patients with LBCL in EPCORE NHL-1, 48 (31%) were ≥ 65 to < 75 years of age and 29 (18%) were ≥ 75 years of age. No clinically meaningful differences in safety or efficacy were observed between patients ≥ 65 years of age compared with younger adult patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of EPKINLY was evaluated in a single-arm study (Study EPCORE NHL-1) in patients with relapsed or refractory LBCL after two or more lines of systemic therapy. The study included patients with DLBCL not otherwise specified, DLBCL arising from indolent lymphoma, high grade B-cell lymphoma, primary mediastinal B-cell lymphoma (PMBCL) and follicular lymphoma Grade 3B (FLG3b). A total of 157 patients received at least one dose of EPKINLY (48 mg) in the expansion phase, which forms the basis of the safety and efficacy analysis for this single arm study.

The median duration of exposure to EPKINLY was 4.1 months (range: 0 to 18 months).

Serious adverse reactions occurred in 57% of patients. Serious adverse reactions (≥ 2%) included CRS, infections (including sepsis, COVID-19, and pneumonia), pleural effusion, febrile neutropenia, pyrexia, 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%). Discontinuation due to adverse reactions occurred in 7.6% of patients. Discontinuations of EPKINLY occurring in two or more patients were COVID-19 or myelodysplastic syndrome (1.3%) each.

Dose delays due to adverse reactions occurred in 34% of patients. The most common (≥2% overall) adverse reactions leading to delay were CRS (n = 11 [7.0%]), neutropenia (n = 7 [4.5%]), thrombocytopenia (n = 4 [2.5%]), pyrexia (n = 4 [2.5%]), and pleural effusion (n = 4 [2.5%]).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

EPCORE NHL-1

Table 8 provides adverse reactions reported in patients with relapsed or refractory LBCL who were assigned to receive the 48 mg full dose and received at least 1 dose of EPKINLY. Adverse reactions are listed by MedDRA body system organ class, rate, and frequency.

Table 8. Adverse Reactions (≥ 5%) Reported in Patients with Relapsed or Refractory LBCL Treated with EPKINLY Monotherapy in Study EPCORE NHL-1

Adverse Reaction by System Organ Class	EPKINLY N = 157	
	All Grades n (%)	Grade ≥ 3 n (%)
Blood and lymphatic system disorders		
Neutropenia[a]	45 (28.7)	34 (21.7)
Anaemia[b]	29 (18.5)	16 (10.2)
Thrombocytopenia[c]	24 (15.3)	11 (7.0)
Cardiac disorders		
Cardiac arrhythmias[d]	18 (11.5)	1 (0.6)
Gastrointestinal disorders		
Abdominal pain[e]	36 (22.9)	3 (1.9)
Diarrhoea	32 (20.4)	0
Nausea	31 (19.7)	2 (1.3)
Constipation	20 (12.7)	0
Vomiting	19 (12.1)	1 (0.6)
General disorders and administration site conditions		
Fatigue[f]	47 (29.9)	5 (3.2)
Injection site reactions[g]	44 (28.0)	0
Pyrexia[h]	37 (23.6)	0
Edema[i]	22 (14.0)	3 (1.9)
Chills	8 (5.1)	0
Pain	8 (5.1)	0
Immune system disorders		
Cytokine release syndrome[j]	78 (49.7)	4 (2.5)
Infections and infestations		
Bacterial infections[k]	28 (17.8)	8 (5.1)
Viral infections[l]	28 (17.8)	9 (5.7)
Pneumonia[m]	13 (8.3)	5 (3.2)
Fungal infections[n]	9 (5.7)	0

Adverse Reaction by System Organ Class	EPKINLY N = 157	
	All Grades n (%)	Grade ≥ 3 n (%)
Investigations		
Alanine aminotransferase increased	9 (5.7)	1 (0.6)
Metabolism and nutrition disorders		
Decreased appetite	19 (12.1)	1 (0.6)
Hypokalaemia	12 (7.6)	1 (0.6)
Hypomagnesaemia	10 (6.4)	0
Hypophosphataemia	8 (5.1)	2 (1.3)
Musculoskeletal and connective tissue disorders		
Back pain	16 (10.2)	1 (0.6)
Arthralgia	11 (7.0)	1 (0.6)
Nervous system disorders		
Headache	21 (13.4)	1 (0.6)
Immune effector cell-associated neurotoxicity syndrome[j]	10 (6.4)	1 (0.6)
Psychiatric disorders		
Insomnia	15 (9.6)	1 (0.6)
Respiratory, thoracic and mediastinal disorders		
Pleural effusion	14 (8.9)	6 (3.8)
Cough	11 (7.0)	0
Dyspnoea	11 (7.0)	3 (1.9)
Skin and subcutaneous tissue disorders		
Rash[o]	23 (14.6)	1 (0.6)
Pruritus	11 (7.0)	0
Vascular disorders		
Hypotension	11 (7.0)	3 (1.9)

Events were graded using NCI CTCAE version 5.0.
[a] Neutropenia includes febrile neutropenia, neutropenia, and neutrophil count decreased.
[b] Anaemia includes anaemia and serum ferritin decreased.
[c] Thrombocytopenia includes platelet count decreased and thrombocytopenia.
[d] Cardiac arrhythmias include atrial fibrillation, bradycardia, long QT syndrome, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, and tachycardia.

Adverse Reaction by System Organ Class	EPKINLY N = 157	
	All Grades n (%)	Grade ≥ 3 n (%)

[e] Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness.
[f] Fatigue includes asthenia, fatigue, and malaise.
[g] Injection site reactions include injection site bruising, 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, and injection site urticaria.
[h] Pyrexia includes body temperature increased and pyrexia.
[i] Edema includes face oedema, generalised oedema, oedema, oedema peripheral, and peripheral swelling.
[j] Events graded using American Society for Transplant and Cellular Therapy consensus criteria.
[k] Bacterial infections include bacterial pyelonephritis, campylobacter gastroenteritis, campylobacter infection, cellulitis, device related infection, enterococcal infection, enterocolitis infectious, escherichia urinary tract infection, folliculitis, gastroenteritis, helicobacter infection, omphalitis, osteomyelitis, pyelonephritis, rash pustular, skin infection, staphylococcal bacteraemia,staphylococcal infection, urinary tract infection, urinary tract infection enterococcal, and urinary tract infection pseudomonal.
[l] Viral infections include asymptomatic COVID-19, bronchitis, COVID-19, cytomegalovirus infection, cytomegalovirus infection reactivation, gastroenteritis viral, herpes simplex, herpes zoster, laryngitis, myringitis, oral herpes, pharyngitis, respiratory syncytial virus infection, rhinovirus infection, sialoadenitis, and upper respiratory tract infection.
[m] Pneumonia includes COVID-19 pneumonia, lower respiratory tract infection, pneumonia, and respiratory tract infection.
[n] Fungal infection includes body tinea, candida infection, oesophageal candidiasis, oral candidiasis, and urinary tract infection fungal.
[o] Rash includes dermatitis bullous, erythema, palmar erythema, penile erythema, rash, rash erythematous, rash maculo-papular, recall phenomenon, seborrheic dermatitis, and skin exfoliation.

8.3 Less Common Clinical Trial Adverse Reactions

Blood and lymphatic system disorders: Lymphopenia (4.5%), leukopenia (3.2%)
Infections and infestations: Sepsis (4.5%)
Immune system disorders: Hypogammaglobulinemia (2.5%)
Metabolism and nutrition disorders: Tumour lysis syndrome (1.3%)
Neoplasms benign, malignant, and unspecified: Tumour flare (2.5%)

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

The following table summarizes treatment-emergent shifts from baseline in laboratory abnormalities in Study EPCORE NHL-1.

Table 9. Laboratory Abnormalities Worsening from Baseline with Grade 3 to 4 Occurring in ≥10% of Patients with Relapsed or Refractory LBCL Treated with EPKINLY Monotherapy in Study EPCORE NHL-1

Laboratory Abnormality[a]	EPKINLY NCI CTAE Grade	
	All Grades (%)[b]	Grade 3 or 4 (%)[b,c]
Lymphocyte count decreased	87.0	77.4
Neutrophils count decreased	50.0	31.8
White blood cells decreased	52.9	22.2
Hemoglobin decreased	62.1	12.4
Platelets decreased	48.4	12.4

a. Percentages based on patients with a baseline and at least one post-baseline assessment for the specific laboratory parameter.
b. N=146 for lymphocyte count decreased; N=148 for neutrophils count decreased; N=153 for white blood cells decreased; N=153 for hemoglobin decreased; N=153 for platelets decreased.
c. Includes shifts from Grade 0-2 at baseline to Grade 3-4 post-baseline and shifts from Grade 3 at baseline to Grade 4 post-baseline.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No formal drug interaction studies have been conducted with EPKINLY.

9.3 Drug-Behavioural Interactions

Drug-behavioral interactions have not been established.

9.4 Drug-Drug Interactions

No formal drug-drug interaction studies have been performed.

EPKINLY causes release of cytokines (see 10.2 Pharmacodynamics) that may suppress activity of CYP enzymes, resulting in increased exposure of CYP substrates. On initiation of EPKINLY therapy in patients being treated with CYP450 substrates with a narrow therapeutic index, therapeutic monitoring CYP substrates should be considered.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Epcoritamab is a humanized IgG1-bispecific antibody that binds to a specific extracellular epitope of CD20 on B cells and to CD3 on T cells. The activity of epcoritamab is dependent upon simultaneous engagement of CD20-expressing cells and CD3-expressing endogenous T cells by epcoritamab that induces specific T-cell activation and T-cell-mediated killing of CD20-expressing cells.

10.2 Pharmacodynamics

Epcoritamab decreases circulating B cells to undetectable level (CD19 B-cell counts < 10 cell/µl) after the first full dose (48 mg) and the decrease was sustained while patients remained on treatment.

Following subcutaneous administration of epcoritamab, transient and modest elevations of circulating levels of selected cytokines (IFN-γ, TNFα, IL-6, IL-2, and IL-10) occurred, mostly after the first full dose (48 mg) with peak levels between 24 and 72 hours. Levels returned to baseline prior to the subsequent full dose.

10.3 Pharmacokinetics

The population pharmacokinetics following subcutaneous administration of epcoritamab was characterized by a two-compartment model with first order subcutaneous absorption and target-mediated drug elimination.

Epcoritamab 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).

Following the recommended SC dose of epcoritamab 48 mg, the geometric mean (% CV) C_{max} of epcoritamab is 10.8 mcg/mL (41.7%) and $AUC_{0\text{-}7d}$ is 68.9 day*mcg/mL (45.1%) at the end of the weekly dosing schedule.

The geometric mean (% CV) C_{max} of epcoritamab is 7.52 mcg/mL (41.1%) and $AUC_{0\text{-}14d}$ is 82.6 day*mcg/mL (49.3%) at the end of q2w schedule.

The geometric mean (% CV) C_{max} of epcoritamab is 4.76 mcg/mL (51.6%) and $AUC_{0\text{-}28d}$ is 74.3 day*mcg/mL (69.5%) at steady state during the q4w schedule.

Absorption

The median (range) T_{max} of epcoritamab 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, based on population PK modeling.

Distribution

The geometric mean (% CV) central volume of distribution is 8.27 L (27.5%), apparent steady-state volume of distribution is 25.6 L (81.8%) and apparent inter-compartmental clearance is 0.5 L/day (72.5%) based on population PK modeling.

Metabolism The metabolism of epcoritamab has not been directly studied. Epcoritamab is expected to be degraded into small peptides and amino acids via catabolic pathways.

Elimination

The geometric mean (% CV) clearance (L/day) is 0.441 (27.8%). The population PK model-derived geometric mean half-life of full dose epcoritamab (48 mg) ranged from 22 to 25 days based on frequency of dosing.

Special Populations and Conditions

No clinically important effects on the pharmacokinetics of epcoritamab were observed based on age (20 to 89 years), sex, race/ethnicity (White, Asian, and Other), mild to moderate renal impairment (CrCl ≥ 30 ml/min to CrCl < 90 mL/min), 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.

No patients with severe renal impairment to end-stage renal disease (CrCl < 30 mL/min) or moderate to severe hepatic impairment (total bilirubin > 1.5 times ULN and any AST) were studied, and therefore the pharmacokinetics of epcoritamab is unknown in these populations.

Body weight has a statistically significant effect on the pharmacokinetics of epcoritamab: Cycle 1 median average concentration was 13% lower in the higher BW group (85 to 144 kg) and 37% higher in the lower BW group (39 to 65 kg) compared to patients with BW of 65 to less than 85 kg, however this effect is not clinically relevant across body weight categories (< 65kg, 65 to < 85, ≥ 85).

- **Pediatrics**

  The pharmacokinetics of epcoritamab in pediatric patients has not been evaluated.

- **Immunogenicity**

  In EPCORE NHL-1 clinical study, 4 of 158 (2.5%) patients who were treated with EPKINLY at the full dose of 48 mg and evaluable for the presence of anti-drug antibodies (ADA) tested positive for anti-epcoritamab antibodies with titers of 1:320 or less. Test for neutralizing antibody was not performed. There was no evidence of an altered pharmacokinetic profile with anti-epcoritamab binding antibody development based on a population PK analysis. There are insufficient data to evaluate the effect of ADA on the safety or efficacy of epcoritamab.

11 STORAGE, STABILITY AND DISPOSAL

Store and transport refrigerated between 2 and 8°C (36 and 46°F).

Keep in the original carton to protect from light. Do not freeze. Do not shake.

Storage for Prepared EPKINLY

Use immediately or store EPKINLY solution in a refrigerator and protect from light up to 24 hours from the time of preparation, between 2 and 8°C (36 and 46°F). Within these 24 hours, EPKINLY solution can be stored for 12 hours at room temperature from the start of dose preparation to administration. Minimize exposure to daylight. Allow EPKINLY solution to equilibrate to room temperature before administration. Discard unused EPKINLY solution beyond the allowable storage time.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name	Epcoritamab (INN)
Chemical name	Recombinant anti-human CD20 and anti-human CD3 bispecific antibody
Molecular formula and molecular mass	Based on the amino acid sequence, the molecular formula of the disulfide bonded epcoritamab molecule without post-translational modifications is $C_{6583}H_{10157}N_{1743}O_{2088}S_{44}$. The predicted molecular weight of unglycosylated epcoritamab is approximately 149 kDa.
Structural formula	Epcoritamab is a glycoprotein belonging to the immunoglobulin (Ig) superfamily, composed of two heavy chains and two light chains.
Physicochemical properties	Clear to slightly opalescent, colorless to slightly yellow liquid

Product Characteristics:

Epcoritamab is manufactured from two biological intermediates, which are produced in Chinese hamster ovary (CHO) cells using recombinant DNA technology.

Epcoritamab has a regular IgG1 structure and biochemical characteristics typical of human IgG1.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Large B-cell Lymphoma (LBCL)

Trial Design and Study Demographics

Table 10. Summary of patient demographics for clinical trials in large B-cell lymphoma (LBCL)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range) Years	Sex n(%)
EPCORE NHL-1	open-label, multi cohort, multicenter, single arm	• Cycle 1: EPKINLY dosing on: ○ Day 1 – 0.16 mg ○ Day 8 – 0.8 mg ○ Day 15 – 48 mg ○ Day 22 – 48 mg • 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	157	62 (20-83)	Female 63 (40) Male 94 (60)

Study EPCORE NHL-1 was an open-label, multi-cohort, multicenter, single-arm trial that evaluated epcoritamab as monotherapy in patients with relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy. The safety and efficacy population included 157 patients with refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified (DLBCL NOS), DLBCL transformed from indolent lymphoma, high grade B-cell lymphoma (HGBCL), primary mediastinal B-cell lymphoma (PMBCL) or follicular lymphoma Grade 3B (FLG3b). The study excluded patients with CNS involvement of lymphoma, allogeneic HSCT or solid organ transplant, ongoing active infectious diseases, any patients with known impaired T-cell immunity, a creatinine clearance of less than 45 mL/min, alanine aminotransferase >3 times the upper limit of normal and cardiac ejection fraction less than 45%.

The median age of patients on study was 64 (range: 20 to 83), 60% were male, 97% had and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and most were either of White (61%) or Asian descent (19%) or were not reported (15%). The median number of prior therapies was 3 (range: 2 to 11), with 29% receiving two prior therapies, 32% receiving 3 prior therapies, and 39% receiving 4 or more prior therapies. Twenty percent of patients had prior autologous hematopoietic stem cell transplants (HSCTs) and 39% had received prior chimeric antigen receptor (CAR) T-cell therapy. Eighty-three percent of patients had disease refractory to their last therapy and 29% were refractory to CAR T-cell therapy.

Patients continued to receive EPKINLY until disease progression or unacceptable toxicity. In the setting of a suspected tumour flare reaction, continued treatment was permitted and subsequent responses to therapy were reported (see Study Results).

Study Results

The primary efficacy endpoint was overall response rate (ORR) determined by Lugano criteria (2014) as assessed by an Independent Review Committee (IRC). The key secondary efficacy outcome measures included IRC assessed complete response (CR) rate, partial response (PR) rate, duration of response (DOR), and duration of complete response (DOCR). The median follow-up time was 10.7 months (range: 0.3 to 17.9 months).

Table 11. Efficacy Results in Study EPCORE NHL-1

Efficacy Endpoints	EPKINLY N=157
Primary Endpoint	
IRC-Assessed Overall Response Rate (ORR)	
Patients with CR or PR, n (%)	99 (63)
95% CI	(55.0, 70.6)
Secondary Endpoints	
Complete Response (CR), n (%)	61 (39)
95% CI	(31.2, 46.9)
Partial Response (PR), n (%)	38 (24)
95% CI	(17.7, 31.7)
Duration of Response (DOR)[a]	
Median (95% CI), months	12 (6.6, NR)
9-month estimate, % (95% CI)	61 (49.3, 70.0)
Duration of Complete Response (DOCR)[b]	
Median (95% CI), months	12 (9.7, NR)
9-month estimate, % (95% CI)	86 (71.8, 93.6)

CI = confidence interval; IRC = independent review committee; a. Determined by Lugano criteria (2014) as assessed by independent review committee (IRC).
a. DOR is defined as the date of first response (PR or CR) until disease progression or death due to any cause.
b. DOCR is defined as the date of first complete response until disease progression or death due to any cause.
Note: 95% CI for response rates were calculated by using Clopper and Pearson method.

Of the 99 patients who had a response to therapy, 10 patients had a tumour flare reaction who continued on therapy as per protocol and had a subsequent partial or complete response (7 PRs and 3 CRs). Among patients who have previously received CAR T-cell therapy, the overall response rate was 54% (33/61) and the complete response rate was 34% (21/61).

The median time to response was 1.4 months (range: 1.0 to 8.4) and the median time to CR was 2.7 months (range: 1.2 to 11.1).

14.4 Immunogenicity

EPKINLY has the potential to induce anti-drug antibodies (ADA). The incidence of antibodies to EPKINLY was low and all the patients who were positive had low titers (≥ 1 in 0.6% [1/158]). Due to the low number of patients with ADAs, a meaningful analysis of the impact of ADAs on safety is limited (see 10.3 Pharmacokinetics).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Animal pharmacology and/or toxicology: Effects generally consistent with the pharmacologic mechanism of action of epcoritamab were observed in cynomolgus monkeys. These findings included dose-related adverse clinical signs (including vomiting, decreased activity, and mortality [at high doses]) and cytokine release, reversible hematologic alterations, reversible B-cell depletion in peripheral blood, and reversible decreased lymphoid cellularity in secondary lymphoid tissues.

Carcinogenicity: Carcinogenicity studies have not been conducted with epcoritamab.

Genotoxicity: Genotoxicity studies have not been conducted with epcoritamab.

Impairment of fertility: Animal fertility studies have not been conducted with epcoritamab.

Reproductive and Developmental Toxicology: Animal reproduction studies have not been conducted with epcoritamab.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrEPKINLY™

Epcoritamab injection (solution for subcutaneous injection) **/ Epcoritamab for injection** (concentrate for solution for subcutaneous injection)

Read this carefully before you start taking **EPKINLY** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **EPKINLY.**

Serious Warnings and Precautions

- Fever (38°C or higher) and chills which may be symptoms of a serious side effect called cytokine release syndrome (CRS), which can be severe or fatal. Other symptoms of CRS may include difficulty in breathing, dizziness or feeling light-headed, feeling the need to throw up, headache, fast heartbeat, low blood pressure, feeling tired, vomiting, muscle pain and joint pain.
- Neurologic problems which may include symptoms like headache, confusion, difficulty with memory, difficulty speaking or slow speech, difficulty understanding speech, difficulty in writing, confused about time or surroundings, being less alert, or excessive sleepiness, and seizures (fits) which can be serious or life-threatening. Some of these may be signs of a serious immune reaction called 'immune effector cell associated neurotoxicity syndrome' (ICANS). These effects can occur days or weeks after you receive the injection, and may not be serious right away.

Your healthcare professional will monitor for signs and symptoms of CRS and neurological problems during treatment with EPKINLY. Call your doctor or get emergency help right away if you develop any of these signs and symptoms of CRS or neurologic problems at any time during your treatment with EPKINLY.

What is EPKINLY used for?

For the following indication(s) EPKINLY has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- EPKINLY is used to treat some forms of large B-cell lymphomas – a cancer of blood cells (cancerous B cells), mostly in the lymph nodes. EPKINLY can be used in adults when the cancerous B cells have returned after other treatments or when other treatments did not work. It may be used if you are not able to receive or have previously received a treatment called CAR-T cell therapy.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does EPKINLY work?

EPKINLY is a cancer medicine (bispecific antibody) that binds to the surface of cancerous B cells and also to the surface of T cells (another type of white blood cell). This binding on two targets activates T cells, which causes them to multiply, and in turn helps kill the cancerous B cells.

What are the ingredients in EPKINLY?

Medicinal ingredients: epcoritamab

Non-medicinal ingredients: acetic acid, polysorbate 80, sodium acetate trihydrate, sorbitol, and water for injection

EPKINLY comes in the following dosage forms:

EPKINLY is available as single-dose vials: 4 mg in 0.8 mL sterile solution (5 mg/mL) or 48 mg in 0.8 mL sterile solution (60 mg/mL).

Do not use EPKINLY if:

- you are allergic to epcoritamab or any of the other ingredients of this medicine (listed in "What are the ingredients in EPKINLY?"). Talk to your doctor before you are given EPKINLY if you are not sure.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take EPKINLY. Talk about any health conditions or problems you may have, including if you:

- have or had problems with your nervous system – such as seizures
- have or had liver, kidney or heart problems
- have an infection
- are due to have a vaccine or you know you may need to have one in the near future
- are pregnant or plan to become pregnant

EPKINLY can cause serious side effects that can be severe or, life-threatening and can lead to death. These side effects include cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS).

Call your doctor or get emergency help right away if you get any of the following:

Cytokine Release Syndrome (CRS). Symptoms may include:

- fever (38°C or higher)
- low blood pressure
- chills
- fast heartbeat
- headache

Immune effector cell-associated neurotoxicity syndrome (ICANS). Effects on your nervous system which can occur days or weeks after you receive the injection and may initially be subtle. Some of these symptoms may be signs of a serious immune reaction called "immune effector cell associated neurotoxicity syndrome" (ICANS). Symptoms of ICANS may include:

- difficulty speaking or writing
- drowsiness
- confusion/disorientation
- muscle weakness
- seizures
- memory loss

If you notice any of these symptoms listed above, call your doctor or nurse right away.

Your doctor may give you medicine to treat your side effects. Your healthcare provider will check for these problems during treatment with EPKINLY.

Other warnings you should know about:

Pregnancy, contraception, breastfeeding and fertility

- Pregnancy must be ruled out before treatment. There is no information about the safety of EPKINLY in pregnant women. Tell your doctor immediately if you become pregnant. If you are a woman of child-bearing potential, use effective contraception during treatment with EPKINLY and for at least 4 months after the last dose of EPKINLY.
- Talk to your doctor or nurse about ways to avoid becoming pregnant.
- You must not breast-feed during treatment with EPKINLY and for 4 months after the last dose. EPKINLY may be passed into breast milk and could potentially harm the baby.
- The effects of EPKINLY on male and female fertility are not known.

Driving and using machines

- EPKINLY may affect your ability to drive, cycle, or use any tools or machines. If you have any symptoms that might make this difficult (such as fever, fast heartbeat, feeling dizzy or lightheaded, chills or shortness of breath, etc.) do not drive, cycle, or use any tools or machines until you feel better.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Interactions between epcoritamab and other drugs, vitamins, minerals, natural supplements or alternative medicines have not been established.

How to take EPKINLY:

Your doctor will give you EPKINLY as an injection under your skin (subcutaneous injection), on a dosing schedule, in 28 day cycles. You will be given EPKINLY according to the following schedule:

Cycle	**Dosing Schedule**
Cycle 1 to 3	Weekly
Cycles 4 to 9	Every other week
Cycles 10 and beyond	Every four weeks

You may be given other medicines before you are given EPKINLY. This is to help prevent reactions such as fever in Cycle 1 (and potentially future Cycles).

These other medicines may include:

- corticosteroids- such as prednisolone or equivalent
- an antihistamine – such as diphenhydramine
- acetaminophen

Usual dose:

Your first two doses are small doses given to you on Day 1 of Cycle 1 (0.16 mg) and Day 8 of Cycle 1 (0.8 mg) to manage side effects of this therapy.

The first full dose (48 mg) of EPKINLY will be given to you on Cycle 1 Day 15. For 24 hours following administration of the first full dose of 48 mg, you should remain within proximity of a healthcare facility. It is also possible that your healthcare professional decides to hospitalize you.

You will be given EPKINLY for as long as your doctor thinks you are benefitting from the treatment.

Your doctor may delay or completely stop your treatment with EPKINLY if you have certain side effects.

Overdose:

If you think you, or a person you are caring for, have taken too much EPKINLY, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss an appointment to have EPKINLY administered, make another one straight away. For the treatment to be fully effective, it is very important not to miss a dose.

What are possible side effects from using EPKINLY?

These are not all the possible side effects you may have when taking EPKINLY. If you experience any side effects not listed here, tell your healthcare professional. You may only get one or some of these symptoms.

Very common (may affect more than 1 in 10 people):

- headache
- bacterial infection such as urinary tract infection
- decreased hunger
- viral infections such as lung infections (pneumonia)
- nausea
- diarrhea
- vomiting
- tiredness
- injection site reactions
- abdominal pain (pain in the belly area)
- back pain
- swelling
- constipation

Shown in blood tests:

- low levels of some white blood cells (neutropenia), which may lead to fever or symptoms of an infection such as chills, sore throat, shortness of breath, congestion, diarrhea
- low number of red blood cells, which can cause tiredness (anemia)
- low platelet count, which may make you more likely to bruise or bleed (thrombocytopenia)
- low levels of potassium in the blood

Common (may affect up to 1 in 10 people):

- pneumonia (lung infection)
- tumour lysis syndrome (a rapid breakdown of tumour cells resulting in chemical changes in the blood and damage to organs, including the kidneys, heart, and liver)
- difficulty sleeping
- extra fluid around the lungs that make it difficult to breathe (pleural effusion)
- increased heart rate
- cough
- difficulty breathing
- pain in bones and joints
- chills
- fungal infections (caused by a type of germ called a fungus)
- rash
- itching
- confusion

Shown in blood tests:

- low level of phosphates in the blood, potassium, magnesium or sodium
- increased blood level of liver proteins, which may show problems with the liver (ALT)

Tell your doctor straight away if you noticed any of the symptoms of the following serious side effects. You may only get one or some of these symptoms.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Cytokine release syndrome (CRS): fever, low blood pressure, chills, fast heartbeat, difficulty breathing, trouble breathing/low blood oxygen levels, headache		√	
COMMON			
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS): difficulty speaking or writing, drowsiness, confusion/disorientation, muscle weakness, seizures, memory loss		√	
Serious infections: fever, chills, difficulty breathing, burning pain when passing urine, confusion		√	
Tumour Lysis Syndrome: kidney problems (weakness, shortness of breath, fatigue, feeling confused), heart problems (irregular heartbeat or fluttering of the heart or a faster or slower heartbeat), vomiting, diarrhea, tingling in the mouth, hands or feet, muscle cramp		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

EPKINLY will be stored by the doctor, nurse, or pharmacist at the hospital or clinic. To correctly store EPKINLY:

Keep this medicine out of the sight and reach of children.

Store and transport refrigerated (2°C to 8°C).

Keep the vial in the original carton in order to protect from light.

Do not freeze. Do not shake.

If you want more information about EPKINLY:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website (www.abbvie.ca), or by calling 1-888-704-8271.

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Instructions For Use

EPKINLY 4 mg/0.8 mL

The following information is intended for healthcare professionals only:

EPKINLY (epcoritamab for injection) 4 mg/0.8 mL vial **must be diluted** using aseptic technique by a healthcare professional.

To prepare EPKINLY priming (0.16 mg) and intermediate (0.8 mg) doses**,** the following table outlines the materials needed for preparation of the priming and intermediate doses.

Materials needed	
Priming Dose	**Intermediate Dose**
4 mg/0.8 mL (5 mg/mL) EPKINLY vial with **light blue** cap	4 mg/0.8 mL (5 mg/mL) EPKINLY vial with **light blue** cap
0.9% Sodium Chloride Injection, USP	0.9% Sodium Chloride Injection, USP
Two empty sterile vials between 10 and 20 mL	One empty sterile vial between 10 and 20 mL
Recommended Syringe Sizes: • Two 1 mL syringes • One 3 mL syringe • One 5 mL syringe • One 10 mL syringe	Recommended Syringe Sizes: • Two 1 mL syringes • One 5 mL syringe

Priming Dose (0.16 mg) Preparation Instructions – Two Separate Dilution Steps Required:

Use a new, appropriately sized, syringe and needle for each transfer step.

1) Prepare EPKINLY vial
   a. Retrieve one 4 mg/0.8 mL (5 mg/mL) EPKINLY (epcoritamab **for injection**) vial with the **light blue** cap 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. Use an empty vial of an appropriate size. Label this vial as **"dilution A"**.
   b. Using a 1 mL syringe, transfer **0.8 mL of EPKINLY** into vial labeled as **dilution A**.
   c. Using a 5 mL syringe, transfer **4.2 mL of 0.9% Sodium Chloride Injection, USP** into vial labeled as **dilution A**.
   d. Gently swirl the **dilution A** vial for 30 – 45 seconds.

At end of first dilution for priming dose, the concentration is 0.8 mg/mL.

3) Perform second dilution
   a. Use the second empty vial of an appropriate size. Label this vial as "**dilution B**".
   b. Using a 3 mL syringe, transfer **2.0 mL of solution** from the vial labeled as **dilution A** into the **dilution B** vial. The **dilution A** vial is no longer needed.

c. Using a 10 mL syringe, transfer **8.0 mL of 0.9% Sodium Chloride Injection, USP** into the **dilution B** vial.
d. Gently swirl the **dilution B** vial for 30 – 45 seconds.

At end of second dilution for priming dose, the concentration is 0.16 mg/mL.

4) Withdraw dose

Using a 1 mL syringe for SC injection, withdraw **1 mL of the solution** from the **dilution B** vial.

5) Label syringe

Label the syringe 0.16 mg and include the time of day.

Discard the single-dose vial and any unused portions of EPKINLY in accordance with local requirements.

Intermediate Dose (0.8 mg) Preparation Instructions – One Dilution Step Required:

Use a new, appropriately sized, syringe and needle for each transfer step.

1) Prepare EPKINLY vial
   a. Retrieve one 4 mg/0.8 mL EPKINLY (epcoritamab **for injection**) vial with the **light blue** cap 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. Use an empty vial of an appropriate size. Label this vial as **"dilution A"**.
   b. Transfer **0.8 mL of EPKINLY** into vial labeled as **dilution A**.
   c. Transfer **4.2 mL of 0.9% Sodium Chloride Injection, USP** into vial labeled as **dilution A**.
   d. Gently swirl the **dilution A** vial for 30 – 45 seconds.

At end of dilution for intermediate dose, the concentration is 0.8 mg/mL.

3) Withdraw dose

Using a 1 mL syringe for SC injection, withdraw **1 mL of the solution** from the **dilution A** vial.

4) Label syringe

Label the syringe 0.8 mg and include the time of day.

Discard the single-dose vial and any unused portions of EPKINLY in accordance with local requirements.

Instructions For Use

EPKINLY 48 mg/0.8 mL

The following information is intended for healthcare professionals only:

DO NOT dilute. EPKINLY (epcoritamab injection) 48 mg/0.8 mL (60 mg/mL) vial is ready to use.

1) Prepare EPKINLY vial
   a. Retrieve one 48 mg/0.8 mL (60 mg/mL) EPKINLY (epcoritamab **injection**) vial with the **orange** cap 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

Withdraw **0.8 mL of the EPKINLY** into a syringe for subcutaneous injection.

3) Label syringe

Label the syringe 48 mg and include the time of day.

Discard the single-dose vial and any unused portions of EPKINLY in accordance with local requirements.