

Product Monograph
Including Patient Medication Information

^{Pr}**EPKINLY**[®]

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>.

EPKINLY, indicated:

- in combination with lenalidomide and rituximab for the treatment of adult patients with relapsed or refractory Grade 1, 2, or 3a follicular lymphoma (FL) who have received at least one prior line of systemic therapy.

has been issued market authorization without conditions.

AbbVie Corporation
8401 Trans-Canada Highway
St-Laurent, QC H4S 1Z1

Date of Authorization:
2026-09-17

Control Number: 307043

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

A 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

1 Indications	2026-09
3 Serious Warnings and Precautions Box	2026-09
4 Dosage and Administration, 4.1 Dosing considerations	2026-09
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	2026-09
4 Dosage and Administration, 4.3 Reconstitution	2026-09
4 Dosage and Administration, 4.5 Missed Dose	2026-09
7 Warnings and Precautions, Immune	2026-09
7 Warnings and Precautions, Serious Infections	2026-09
7 Warnings and Precautions, Neurologic	2026-09
7 Warnings and Precautions, 7.1 Special Populations, 7.1.4 Geriatrics	2026-09

Table of Contents

Certain sections (as indicated in section 2.1. of the PM Guidance) or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Recent Major Label Changes	2
Table of Contents	2
Part 1: Healthcare Professional Information	5
1. Indications	5
1.1. Pediatrics	5
1.2. Geriatrics	5
2. Contraindications	5
3. Serious Warnings and Precautions Box	5

4. Dosage and Administration	6
4.1. Dosing Considerations	6
4.2. Recommended Dose and Dosage Adjustment	8
For patients with relapsed or refractory diffuse large B-cell lymphoma	8
For patients with relapsed or refractory follicular lymphoma, in combination with lenalidomide and rituximab	9
4.3. Reconstitution	11
4.4. Administration	14
4.5. Missed Dose	14
Diffuse large B-cell lymphoma	14
Follicular lymphoma	15
5. Overdose	16
6. Dosage Forms, Strengths, Composition, and Packaging	16
7. Warnings and Precautions	16
Driving and Operating Machinery	17
Endocrine and Metabolism	17
Hepatic/Biliary/Pancreatic	17
Immune	17
Cytokine Release Syndrome	17
Serious Infections	20
Cytopenias	20
Vaccines	20
Neurologic	21
Renal	24
Reproductive Health	24
7.1. Special Populations	24
7.1.1. Pregnancy	24
7.1.2. Breastfeeding	25
7.1.3. Pediatrics	25
7.1.4. Geriatrics	25
8. Adverse Reactions	25
8.1. Adverse Reaction Overview	25

8.2.	Clinical Trial Adverse Reactions	27
8.3.	Less Common Clinical Trial Adverse Reactions	32
8.4.	Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data	33
8.5.	Post-Market Adverse Reactions.....	34
9.	Drug Interactions.....	34
9.2.	Drug Interactions Overview	34
9.3.	Drug-Behaviour Interactions.....	35
9.4.	Drug-Drug Interactions	35
9.5.	Drug-Food Interactions	35
9.6.	Drug-Herb Interactions	35
9.7.	Drug-Laboratory Test Interactions.....	35
10.	Clinical Pharmacology.....	35
10.1.	Mechanism of Action	35
10.2.	Pharmacodynamics.....	35
10.3.	Pharmacokinetics.....	35
10.4.	Immunogenicity	37
11.	Storage, Stability, and Disposal	37
	Part 2: Scientific Information	38
13.	Pharmaceutical Information	38
14.	Clinical Trials	39
14.1.	Clinical Trials by Indication	39
	Large B-cell lymphoma (LBCL).....	39
	Follicular lymphoma.....	41
15.	Microbiology	44
16.	Non-Clinical Toxicology	44
	Patient Medication Information	45

Part 1: Healthcare 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.
- In combination with lenalidomide and rituximab for the treatment of adult patients with relapsed or refractory Grade 1, 2, or 3a follicular lymphoma (FL) who have received at least one prior line of systemic 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): In patients with LBCL, no clinically meaningful differences in safety or efficacy were observed between patients ≥ 65 years of age compared with younger adult patients.

In patients with FL, no clinically meaningful differences in efficacy were observed between patients ≥ 65 years of age compared with younger adult patients. A higher incidence of serious and fatal treatment-emergent adverse events was observed in patients ≥ 65 years of age compared to younger patients (see [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](#)).

- **Progressive Multifocal leukoencephalopathy (PML)**, which include life-threatening and fatal events have occurred in patients receiving EPKINLY. Withhold EPKINLY if PML is suspected and permanently discontinue if PML is confirmed (see [7 Warnings and Precautions](#)).
- **Haemophagocytic lymphohistiocytosis (HLH)**, including fatal cases, have been reported in patients receiving EPKINLY, and in some instances HLH has been reported independently of CRS (see [7 Warnings and Precautions](#)).

Patients with DLBCL should be monitored in proximity to a healthcare facility 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

- Counsel patients on the risks associated with EPKINLY and distribute the Patient Card prior to administration of the first step-up dose (SUD).
- 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](#)).
- Certain doses of EPKINLY require **dilution** prior to administration (see [4.2 Recommended Dose and Dosage Adjustment](#) and [4.3 Reconstitution](#)).

Premedication and Prophylaxis

- Prophylaxis against *Pneumocystis jirovecii pneumonia* (PJP) and herpes virus infections is strongly recommended during 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 ^a	Administration
Cycle 1	All patients	Dexamethasone^b (15mg oral or intravenous) or 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 ^c CRS with previous dose	Dexamethasone^b (15mg oral or intravenous) or Prednisolone (100 mg oral or IV) or equivalent	30-120 minutes prior to next administration of EPKINLY after a grade 2 or 3^c 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. Premedication used for combination agents may also serve as premedication for EPKINLY at the discretion of the treating physician, provided that the doses administered are at least equivalent. b. Dexamethasone is the preferred corticosteroid for CRS prophylaxis. c. 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. 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](#)). For patients with DLBCL, 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. For patients with FL, the duration of monitoring following the first full dose of 48 mg (Day 22 of Cycle 1) may vary based on individual patient risk factors (see [7 Warnings and Precautions](#)).

4.2. Recommended Dose and Dosage Adjustment

For patients with relapsed or refractory diffuse large B-cell lymphoma

- EPKINLY is administered by subcutaneous (SC) injection only in 28-day cycles with 2 step-up doses.
- Patients receive a step-up dose 1 on Day 1 (0.16 mg) and step-up dose 2 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 through 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 for Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Cycle of treatment ^a	Dosing Schedule	Days	EPKINLY Dose	
Cycle 1	Weekly	1	Step-up dose 1	0.16 mg ^b
		8	Step-up dose 2	0.8 mg ^b
		15	First full dose	48 mg
		22	Full dose	48 mg
Cycles 2 and 3	Weekly	1, 8, 15, 22	Full dose	48 mg
Cycles 4 to 9	Every two weeks	1, 15		48 mg
Cycles 10+	Every four weeks	1		48 mg

a. A cycle is 28 days.

b. 0.16 mg and 0.8 mg are step-up doses and 48 mg is a full dose.

For patients with relapsed or refractory follicular lymphoma, in combination with lenalidomide and rituximab

- EPKINLY is administered by subcutaneous (SC) injection only in 28-day cycles for a fixed duration of treatment with 3 step-up doses, for a total of 12 cycles or until disease progression or unacceptable toxicity, whichever occurs first.
- Patients receive step-up dose 1 on Day 1 (0.16 mg), step-up dose 2 on Day 8 (0.8 mg), and step-up dose 3 on Day 15 (3 mg) of Cycle 1 using the 4 mg/0.8 mL (5 mg/mL) EPKINLY vial with light blue cap. Step-up dose 1 and 2 **require dilution** before administration, while step-up dose 3 is **not** diluted (see [4.3 Reconstitution](#) and [4.4 Administration](#)).
- The first **full** EPKINLY dose (48 mg) is taken on Day 22 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 through Cycle 12, the 48 mg EPKINLY doses are administered once every four weeks (Day 1 of each 28-day cycle).
- Administer lenalidomide 20 mg orally once daily (from Day 1 to Day 21) in Cycles 1-12 and rituximab 375 mg/m² intravenously every week in Cycle 1 (on Days 1, 8, 15, and 22) and every 4 weeks in Cycles 2-5 (on Day 1). On days when lenalidomide and rituximab are co-administered, consider administering lenalidomide and rituximab prior to EPKINLY. Lenalidomide dose should be reduced for patients with renal impairment (see [14.1 Clinical Trials by Indication, Follicular lymphoma](#)).

Table 3. Dosing Schedule for Patients with Relapsed or Refractory Follicular Lymphoma, in Combination with Lenalidomide and Rituximab

Cycle of treatment ^a	Dosing Schedule	Days	EPKINLY Dose	
Cycle 1	Weekly	1	Step-up dose 1	0.16 mg ^b
		8	Step-up dose 2	0.8 mg ^b
		15	Step-up dose 3	3 mg ^b
		22	First full dose	48 mg
Cycles 2 and 3	Weekly	1, 8, 15, 22	Full dose	48 mg
Cycles 4 to 12	Every four weeks	1		48 mg

a. A cycle is 28 days.
b. 0.16 mg, 0.8 mg and 3 mg are step-up doses and 48 mg is a full dose.

Table 4. Recommended Dose Modifications for Adverse Reactions

Adverse Reaction	Severity	Action
CRS (including HLH) (see 7 Warnings and Precautions)	Grades 1-3	• Withhold EPKINLY until resolution of CRS/HLH event. • Refer to 4.5 Missed Dose for how to properly resume treatment.

Adverse Reaction	Severity	Action
	Grade 4	Permanently discontinue EPKINLY.
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.
PML	All Grade	- If neurological symptoms suggestive of PML occur during EPKINLY therapy, should be withheld and appropriate diagnostic measures initiated. - Discontinue EPKINLY if PML is confirmed.
Neutropenia or febrile neutropenia ¹ (see 8 Adverse Reactions)	Absolute neutrophil count less than $0.5 \times 10^9/L$	- Consider granulocyte colony-stimulating factor (G-CSF) - Withhold EPKINLY until absolute neutrophil count is $0.5 \times 10^9/L$ or higher. - Refer to 4.5 Missed Dose for how to properly resume treatment.
Thrombocytopenia ¹ (see 8 Adverse Reactions)	Platelet count less than $50 \times 10^9/L$	- Withhold EPKINLY until platelet count is $50 \times 10^9/L$ 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)

Dose adjustments are not considered necessary for EPKINLY based on age.

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

Dose Preparation

Read this entire section carefully before preparation of EPKINLY. Certain doses of EPKINLY require **dilution** prior to administration.

Use aseptic techniques to prepare EPKINLY. DO NOT filter the diluted solution because of potential loss of active ingredient.

The following table outlines the materials needed for preparation of the step-up doses.

Table 5. Materials Needed for Preparation of the Step-up Doses

Materials needed	
Step-Up Dose 1 (0.16 mg)	Step-Up Dose 2 (0.8 mg)
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:	Recommended Syringe Sizes:
- Two 1 mL syringes - One 3 mL syringe - One 5 mL syringe - One 10 mL syringe	- Two 1 mL syringes - One 5 mL syringe

Step-Up Dose 1 (0.16 mg) Preparation Instructions – (2 dilutions required):

Use an appropriately sized syringe, vial 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) Label an appropriately sized empty vial as “Dilution A”. b) Using a 1 mL syringe, transfer 0.8 mL of EPKINLY into the Dilution A vial. c) Using a 5 mL syringe, transfer 4.2 mL of 0.9% Sodium Chloride Injection, sterile solution, into the Dilution A vial. d) Gently swirl the Dilution A vial for 30 – 45 seconds. At end of the first dilution for step-up dose 1, the concentration is 0.8 mg/mL.
3) Perform second dilution a) Label an appropriately sized empty vial as “Dilution B”. b) Using a 3 mL syringe, transfer 2.0 mL of solution from the Dilution A vial 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, sterile solution, into the Dilution B vial. d) Gently swirl the Dilution B vial for 30 – 45 seconds. At end of the second dilution for step-up dose 1, the concentration is 0.16 mg/mL.
4) Withdraw dose a) Using a 1 mL syringe for SC injection, withdraw 1 mL of EPKINLY from the Dilution B vial.
5) Label syringe Label the syringe 0.16 mg and include the time of day.

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

Use prepared EPKINLY immediately or store EPKINLY solution in the syringe in a refrigerator and protect from light up to 24 hours from the time of preparation (see [11 Storage, Stability and Disposal](#)).

Step-Up Dose 2 (0.8 mg) Preparation Instructions – (1 dilution required):

Use an appropriately sized syringe, vial 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) 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, sterile solution , into the Dilution A vial .
d) Gently swirl the Dilution A vial for 30 – 45 seconds.
At end of the dilution for step-up dose 2, the concentration is 0.8 mg/mL.
3) Withdraw dose
a) Using a 1 mL syringe for SC injection, withdraw 1 mL of EPKINLY from the Dilution A vial .
4) Label syringe
Label the syringe 0.8 mg and include the time of day.

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

Use prepared EPKINLY immediately or store EPKINLY solution in the syringe in a refrigerator and protect from light up to 24 hours from the time of preparation (see [11 Storage, Stability and Disposal](#)).

Step-Up Dose 3 (3 mg) Preparation Instructions – (No dilution required):

EPKINLY 3 mg 3rd step-up dose is required for FL patients only (see [4 Dosage and Administration](#)).

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) Withdraw dose
Withdraw 0.6 mL of EPKINLY into a syringe
3) Label syringe
Label the syringe 3mg and include the time of day

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

48 mg Full Dose Preparation Instructions – (No dilution required):

EPKINLY 48 mg/0.8 mL (60 mg/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 (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 EPKINLY into a syringe.
3) Label syringe
Label the syringe 48 mg and include the time of day.

Discard the 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. Each vial of EPKINLY is intended for single dose only.

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](#).

EPKINLY should be inspected visually for particulate matter and discoloration prior to administration.

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 6. Recommendations for Restarting Therapy with EPKINLY After Dosage Delay

Diffuse large B-cell lymphoma

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.

Last Dose Administered	Time Since the Last Dose Administered	Action for Next Dose(s) ^a
	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](#)).

Follicular lymphoma

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 3 mg the week after, then one full dose 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	More than 8 days	Repeat 0.16 mg, then administer 0.8 mg the following week, followed by 3 mg the week after, then one full dose of 48 mg. Then resume the planned dosage schedule beginning with Day 1 of the subsequent cycle.
3 mg on Cycle 1 Day 15	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 3 mg the week after, then one full dose of 48 mg. Then resume the planned dosage schedule beginning with Day 1 of the subsequent cycle.
48 mg on Cycle 1 Day 22 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 3 mg the week after, then one full dose 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. Overdose

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

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 7. 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

Description

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 for step-up dose 1 and 2.
- 48 mg per 0.8 mL (60 mg/mL) single dose vial

The vial stopper is not made from natural rubber latex (made of bromobutyl rubber).

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.

For patients with large B-cell lymphoma (LBCL) in study EPCORE NHL-1, 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.

For patients with follicular lymphoma in EPCORE FL-1 treated with EPKINLY at the recommended 3-step SUD schedule in combination with lenalidomide and rituximab, the median time to onset of CRS from the most recently administered EPKINLY dose across all doses was 78 hours (range: 0.2 to 12 days). The median time to onset after the first full 48 mg dose was 41 hours (range: 0.3 to 12 days). The median duration of CRS events was 2 days (range: 0.1 to 26 days).

Monitor patients for CRS following EPKINLY administrations during Cycle 1 and in subsequent cycles as needed at the discretion of the health professional. 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 8](#). 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.

For patients with DLBCL, 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. For patients with FL, the duration of monitoring following the first full dose of 48 mg (Day 22 of Cycle 1) may vary based on individual patient risk factors.

Management of CRS may require either temporary delay or discontinuation of EPKINLY based on the severity of CRS as per recommendations in [Table 8](#). Patients who experience CRS should be monitored more frequently during the next scheduled EPKINLY administration. Withhold or discontinue EPKINLY as indicated in [Table 4](#) (see [4 Dosage and Administration](#)).

Haemophagocytic lymphohistiocytosis (HLH), including fatal cases, have been reported in patients receiving EPKINLY, and in some instances HLH has been reported independently of CRS. HLH should be considered when the presentation of CRS is atypical or unresponsive and/or when clinical manifestations of HLH present such as prolonged fever, cytopenias, hyperferritinemia, coagulopathy and elevated liver enzymes. If HLH is suspected, withhold EPKINLY and initiate treatment for HLH per current practice guidelines.

Table 8. CRS Grading and Management in Clinical Trials with EPKINLY^a

Grade	Recommended Therapy
Grade 1 Fever (temperature $\geq 38^{\circ}\text{C}$) 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. In case of concurrent ICANS choose alternative to tocilizumab (e.g., siltuximab, anakinra). See Table 9. Corticosteroids: Consider dexamethasone 10-20 mg per day (or equivalent). In case of concurrent ICANS, initiation of corticosteroids is highly recommended.
Grade 2^b Fever (temperature $\geq 38^{\circ}\text{C}$) AND	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.

Grade	Recommended Therapy
- Hypotension not requiring vasopressors. AND/OR - Hypoxia requiring low-flow (≤ 6 L/minute) nasal cannula or blow-by	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 9. 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 $\geq 38^{\circ}\text{C}$) 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 9. Corticosteroids: Dexamethasone (e.g., 10-20 mg IV every 6 hours). If no response, initiate methylprednisolone 1000 mg/day.
Grade 4 - Fever (temperature $\geq 38^{\circ}\text{C}$) 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 9. Corticosteroids:

Grade	Recommended Therapy
	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.

Hypogammaglobulinemia has also been reported in patients receiving EPKINLY. Monitor immunoglobulin levels during treatment with EPKINLY and treat with subcutaneous or intravenous immunoglobulin (IVIG) therapy as clinically indicated. Infection precautions, and antimicrobials, including antibiotic or antiviral prophylaxis, should be used according to local institutional guidelines.

Cases of progressive multifocal leukoencephalopathy (PML), including fatal cases, have been reported in patients treated with EPKINLY. If neurological symptoms suggestive of PML occur during EPKINLY therapy, treatment with EPKINLY should be withheld and appropriate diagnostic measures initiated. Discontinue EPKINLY if PML is confirmed.

Avoid administration of EPKINLY in patients with clinically significant active systemic infections. As appropriate, administer prophylactic antimicrobials and consider surveillance testing for reactivation during treatment with EPKINLY (see [4 Dosage and Administration](#)). Monitor patients for signs and symptoms of infections prior to and during treatment and treat according to standard/local guidelines and practice.

Cytopenias

EPKINLY can cause serious or severe cytopenias, including neutropenia, lymphopenia, anemia, and thrombocytopenia (see [8 Adverse Reactions](#)).

Monitor complete blood counts throughout treatment. Based on the severity of cytopenias, temporarily withhold or permanently discontinue EPKINLY (see [4.2 Recommended Dose and Dosage Adjustment](#)). Consider prophylactic granulocyte colony-stimulating factor administration as applicable.

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.

For patients with LBCL in study EPCORE NHL-1, 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. 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 9](#). For patients with DLBCL, 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. For patients with FL, the duration of monitoring following the first full dose of 48 mg (Day 22 of Cycle 1) may vary based on individual patient risk factors.

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 4](#) (see [4 dosage and administration](#)).

Table 9. ICANS Grading and Management in Clinical Trials with EPKINLY¹

Grade ^a	Recommended Therapy
Grade 1 ICE score ^c 7-9 ^b OR depressed level of consciousness ^b : awakens spontaneously	Dexamethasone, 10 mg IV every 12 hours Consider non-sedating anti-seizure medication (e.g., levetiracetam) until resolution of ICANS <u>Anticytokine therapy</u> <i>No concurrent CRS:</i> Anticytokine therapy not recommended. <i>Concurrent CRS:</i> 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

Grade ^a	Recommended Therapy
	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 ICE score^c 3-6 OR depressed level of consciousness^b: awakens to voice	Dexamethasone at 10-20 mg IV every 12 hours Consider non-sedating anti-seizure medication (e.g., levetiracetam) until resolution of ICANS. <u>Anticytokine therapy:</u> <i>No concurrent CRS:</i> Anticytokine therapy not recommended. <i>Concurrent CRS:</i> 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 ICE score^c 0-2 OR depressed level of consciousness^b: awakens only to tactile stimulus, OR seizures^b, either: - any clinical seizure, focal or generalized that resolves rapidly, or - non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, OR	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> <i>No concurrent CRS:</i> Anticytokine therapy not recommended. <i>Concurrent CRS:</i> 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 ^a	Recommended Therapy
raised intracranial pressure: focal/local oedema^b on neuroimaging^c	
Grade 4 ICE score^{c, b} 0 OR depressed level of consciousness^b either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma OR seizures^b, either: • life-threatening prolonged seizure (> 5 minutes), or • repetitive clinical or electrical seizures without return to baseline in between OR motor findings^b:	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> <i>No concurrent CRS:</i> Anticytokine therapy not recommended. <i>Concurrent CRS:</i> 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 ^a	Recommended Therapy
• deep focal motor weakness such as hemiparesis or paraparesis, or raised intracranial pressure / cerebral oedema^b, with signs/symptoms such as: ○ diffuse cerebral oedema on neuroimaging, or ○ decerebrate or decorticate posturing, or ○ cranial nerve VI palsy, or • papilloedema, or • Cushing's triad	
1. The recommendations describe management of ICANS in Study EPCORE NHL-1. Treat ICANS per institutional guidelines. a. ICANS graded according to ASTCT ICANS Consensus Grading. b. ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizures, motor findings, raised ICP/cerebral oedema) 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 (name 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.	

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

• 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. Pregnancy

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. Breastfeeding

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 who received EPKINLY 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 were observed between patients ≥ 65 years of age compared with younger adult patients.

In patients with relapsed or refractory FL who received EPKINLY in combination with lenalidomide and rituximab in the EPCORE FL-1 study, 155 (64%) were < 65 years of age, 68 (28%) were ≥ 65 to < 75 years of age and 20 (8.2%) were ≥ 75 years of age. Serious adverse events were reported in 82 (52.9%), 41 (60.3%) and 12 (60.0%) patients, and fatal adverse events in 2 (1.3%), 3 (4.4%) and 1 (5.0%) patients, in these age subgroups, respectively.

8. Adverse Reactions

8.1. Adverse Reaction Overview

Large B-cell lymphoma

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 ($\geq 2\%$ 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%]).

Follicular lymphoma

The safety of EPKINLY in combination with lenalidomide and rituximab was evaluated in an open-label, randomized, multicenter study (Study EPCORE FL-1) in patients with relapsed or refractory FL after one prior line of therapy. Patients received EPKINLY in combination with lenalidomide and rituximab (N=243) or lenalidomide and rituximab alone (N=238). See [14.1 Clinical Trials by Indication](#).

With the exception of CRS and ICANS, the safety results presented below and in Table 11 represent data from 243 patients who received EPKINLY following the 2-step SUD schedule or the recommended 3-step SUD schedule in combination with lenalidomide and rituximab. The data presented for CRS and ICANS reflect the 133 patients who received EPKINLY at the recommended 3-step SUD schedule in combination with lenalidomide and rituximab.

Of the 133 patients who received EPKINLY at the recommended 3-step SUD schedule in combination with lenalidomide and rituximab, CRS occurred in 26% of patients, with Grade 1 CRS occurring in 21% and Grade 2 in 5% of patients. Serious adverse reactions due to CRS occurred in 12% of patients who received EPKINLY in combination with lenalidomide and rituximab. Dose delays (interruptions) of EPKINLY due to CRS occurred in 11% of patients.

Of the 243 patients who received EPKINLY in combination with lenalidomide and rituximab, the median duration of exposure for EPKINLY, lenalidomide, and rituximab, was 12 (range: 1 to 12), 12 (range: 1 to 12), and 5 (range: 1 to 8) cycles, respectively.

Of the 243 patients who received epcoritamab following the 2-step SUD schedule or recommended 3-step SUD schedule in combination with lenalidomide and rituximab, the most common ($\geq 20\%$) adverse reactions were neutropenia (74%), rash (43%), upper respiratory tract infections (35%), CRS (35%), fatigue (33%), diarrhea (31%), injection site reactions (28%), anemia (28%), constipation (28%), thrombocytopenia (28%), hypogammaglobulinemia (25%), COVID-19 (24%), pyrexia (24%), and pneumonia (24%). Serious adverse reactions occurred in 44% of patients who received epcoritamab in combination with lenalidomide and rituximab. Serious adverse reactions in $\geq 5\%$ of patients included CRS (19%), pneumonia (15%), COVID-19 (7.8%), and febrile neutropenia (5.3%). Fatal adverse events were reported in 1.6% of patients.

Permanent discontinuation of EPKINLY due to an adverse reaction occurred in 8.6% of patients who received EPKINLY in combination with lenalidomide and rituximab. Adverse reactions which resulted in permanent discontinuation of EPKINLY in more than 1 patient included pneumonia, COVID-19, upper respiratory tract infections, and neutropenia.

Dose delays of EPKINLY due to an adverse reaction occurred in 76.1% of patients who received EPKINLY in combination with lenalidomide and rituximab. Adverse reactions which resulted in dose delays of EPKINLY in $\geq 5\%$ of patients included neutropenia, upper respiratory tract infections, COVID-19, pneumonia, CRS, rash, and thrombocytopenia.

In the EPKINLY arm, adverse reactions led to lenalidomide dose interruption in 74.5%, dose reduction in 23.5%, and permanent discontinuation in 18.5% of patients. Adverse events led to rituximab dose interruption in 60.1% and permanent discontinuation in 2.9% of patients.

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 10 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 10. 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	44 (28.0)	33 (21.0)
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

Adverse Reaction by System Organ Class	EPKINLY N = 157	
	All Grades n (%)	Grade ≥ 3 n (%)
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
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 ^l	10 (6.4)	1 (0.6)
Psychiatric disorders		
Insomnia	15 (9.6)	1 (0.6)

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

EPCORE FL-1

Table 11. provides adverse reactions reported in patients with relapsed or refractory FL who received EPKINLY in combination with lenalidomide and rituximab with a difference between Arms of $\geq 5\%$ for all Grades or $\geq 2\%$ for Grade 3 or 4 in EPCORE FL-1

Table 11. Adverse Reactions in Patients with Relapsed or Refractory FL Who Received EPKINLY in Combination with Lenalidomide and Rituximab with a Difference Between Arms of $\geq 5\%$ for All Grades or $\geq 2\%$ for Grade 3 or 4 in EPCORE FL-1

Adverse Reaction [§]	EPKINLY + Lenalidomide and Rituximab (N=243)		Lenalidomide and Rituximab (N=238)	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
Blood and lymphatic system disorders				
Neutropenia ^a	180 (74.1)	167 (68.7)	123 (51.7)	100 (42.0)
Thrombocytopenia ^b	67 (27.6)	23 (9.5)	44 (18.5)	15 (6.3)
Anemia ^c	68 (28.0)	19 (7.8) [#]	41 (17.2)	11 (4.6)
Lymphopenia ^d	42 (17.3)	31 (12.8)	25 (10.5)	10 (4.2)
Febrile neutropenia	15 (6.2)	15 (6.2)	6 (2.5)	6 (2.5)
Gastrointestinal disorders				
Diarrhea	75 (30.9)	10 (4.1) [#]	60 (25.2)	7 (2.9) [#]
Constipation	67 (27.6)	2 (0.8) [#]	51 (21.4)	0
Nausea	41 (16.9)	0	28 (11.8)	1 (0.4) [#]
Mucositis ^e	24 (9.9)	0	8 (3.4)	0
General disorders and administration site conditions				
Fatigue ^f	80 (32.9)	13 (5.3) [#]	59 (24.8)	5 (2.1) [#]
Injection site reactions ^g	68 (28.0)	0	1 (0.4)	0
Pyrexia	58 (23.9)	1 (0.4) [#]	33 (13.9)	3 (1.3) [#]
Immune system disorders				
Hypogammaglobulinemia ^m	60 (24.7)	1 (0.4)	11 (4.6)	0
Cytokine release syndrome ^{†‡}	35 (26.3)	0	1 (0.4)	0
Infections and infestations				
Upper respiratory tract infections ^h	86 (35.4)	11 (4.5)	55 (23.1)	2 (0.8) [#]
COVID-19 ⁱ	58 (23.9)	14 (5.8) [#]	33 (13.9)	4 (1.7) [#]

Adverse Reaction [§]	EPKINLY + Lenalidomide and Rituximab (N=243)		Lenalidomide and Rituximab (N=238)	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
Pneumonia ^j	57 (23.5)	40 (16.5)	22 (9.2)	13 (5.5)
Cytomegalovirus infection ^k	18 (7.4)	5 (2.1) [#]	3 (1.3)	0
Herpes virus infection ^l	18 (7.4)	2 (0.8) [#]	2 (0.8)	0
Investigations				
Blood potassium decreased ⁿ	48 (19.8)	16 (6.6) [#]	21 (8.8)	6 (2.5)
Alanine aminotransferase increased	46 (18.9)	15 (6.2) [#]	23 (9.7)	2 (0.8) [#]
Aspartate aminotransferase increased	29 (11.9)	5 (2.1) [#]	15 (6.3)	3 (1.3) [#]
Nervous system disorders				
Neurological changes ^o	30 (12.3)	0	13 (5.5)	0
Headache	27 (11.1)	0	9 (3.8)	0
Psychiatric disorders				
Insomnia	35 (14.4)	0	8 (3.4)	0
Skin and subcutaneous tissue disorders				
Rash ^p	105 (43.2)	26 (10.7) [#]	80 (33.6)	14 (5.9) [#]
[§] Adverse reactions were graded based on CTCAE Version 5.0. [†] The frequency of CRS is based on 133 patients with FL who received EPKINLY at the recommended 3-step SUD schedule in combination with lenalidomide and rituximab in EPCORE FL-1 vs 238 patients with FL who received lenalidomide and rituximab [‡] CRS was graded using ASTCT consensus criteria (Lee et al., 2019). [#] Only grade 3 adverse reactions occurred. ^a Neutropenia includes neutropenia, neutrophil count decreased. ^b Thrombocytopenia includes platelet count decreased, thrombocytopenia. ^c Anemia includes anaemia, serum ferritin decreased. ^d Lymphopenia includes lymphocyte count decreased, lymphopenia. ^e Mucositis includes aphthous ulcer, mouth ulceration, mucosal infection, mucosal inflammation, oropharyngeal pain, stomatitis. ^f Fatigue includes asthenia, fatigue, lethargy, malaise. ^g Injection site reactions includes injection site cellulitis, injection site erythema, injection site inflammation, injection site nodule, injection site pain, injection site pruritus, injection site reaction, injection site swelling. ^h Upper respiratory tract infections includes acute sinusitis, laryngitis, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, rhinitis, rhinovirus infection, sinusitis, upper respiratory tract infection. ⁱ COVID-19 includes COVID-19, COVID-19 pneumonia, coronavirus infection, coronavirus pneumonia.				

Adverse Reaction [§]	EPKINLY + Lenalidomide and Rituximab (N=243)		Lenalidomide and Rituximab (N=238)	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
^j Pneumonia includes atypical pneumonia, bronchopulmonary aspergillosis, infective exacerbation of bronchiectasis, <i>pneumocystis jirovecii</i> pneumonia, pneumonia, pneumonia acinetobacter, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia fungal, pneumonia haemophilus, pneumonia influenza, pneumonia legionella, pneumonia mycoplasmal, pneumonia parainfluenzae viral, pneumonia pneumococcal, pneumonia pseudomonal, pneumonia respiratory syncytial viral, pneumonia viral. ^k Cytomegalovirus infection includes cytomegalovirus chorioretinitis, cytomegalovirus colitis, cytomegalovirus infection, cytomegalovirus infection reactivation, cytomegalovirus viraemia. ^l Herpesvirus infection includes congenital herpes simplex infection, herpes simplex, herpes simplex reactivation, herpes virus infection, herpes zoster, oral herpes, varicella zoster virus infection. ^m Hypogammaglobulinaemia includes blood immunoglobulin G decreased, hypogammaglobulinaemia, hypoglobulinaemia, immunoglobulins decreased. ⁿ Blood potassium decreased includes hypokalaemia. ^o Neurological changes includes balance disorder, brain fog, cognitive disorder, confusional state, disturbance in attention, dysphonia, essential tremor, hypoacusis, memory impairment, tremor, vertigo. ^p Rash includes application site rash, blister, catheter site rash, dermatitis, erythema, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin reaction, toxic skin eruption, urticaria.				

In EPCORE FL-1, CRS of any grade occurred in 26% (35/133) of patients treated with EPKINLY at the recommended 3-step SUD schedule in combination with lenalidomide and rituximab. The incidence of Grade 1 CRS was 21% (28/133) and Grade 2 was 5.3% (7/133). At the time of analysis, there were no Grade ≥ 3 CRS events reported.

Recurrent CRS occurred in 10% (13/133) of patients. Of all the CRS events, most (88%) occurred during Cycle 1. In Cycle 1, CRS occurred in 6% (8/133) of patients after the step-up dose 1 (Cycle 1 Day 1), 3.8% (5/133) of patients after the step-up dose 2 (Cycle 1 Day 8), 2.3% (3/132) of patients after the step-up dose 3 (Cycle 1 Day 15), and 19% (25/132) of patients after the first full dose (Cycle 1 Day 22). The median time to onset of CRS from the most recently administered EPKINLY dose across all doses was 78 hours (range: 0.2 to 12 days). The median time to onset after the first full 48 mg dose was 41 hours (range: 0.3 to 12 days). All CRS events resolved and the median duration of CRS events was 2 days (range: 0.1 to 26 days).

ICANS occurred in 0.8% (1/133) of patients with FL treated with EPKINLY at the recommended 3-step SUD schedule in combination with lenalidomide and rituximab, with a single event reported as Grade 1. The event occurred after the 48 mg dose on Cycle 1 Day 22 and ICANS resolved in 3 days.

Serious infections were reported in 33% (81/243) of patients with FL treated with EPKINLY in combination with lenalidomide and rituximab. The most common were pneumonia (10%), COVID-19 (4.5%), and COVID-19 pneumonia (3.7%).

8.3. Less Common Clinical Trial Adverse Reactions

For large B-cell lymphoma

Blood and lymphatic system disorders: Lymphopenia (4.5%), leukopenia (3.2%), febrile neutropenia (2.5%)

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%)

For follicular lymphoma

Nervous system disorders: Immune effector cell-associated neurotoxicity syndrome (0.8%, among subjects who received the 3-step SUD schedule)

Infections and infestations: Sepsis (0.4%)

Metabolism and nutrition disorders: Tumour lysis syndrome (0.4%)

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

Clinical Trial Findings for EPCORE NHL-1

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

Table 12. 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.		

Clinical Trial Findings for EPCORE FL-1

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

Table 13. Laboratory Abnormalities (≥ 30% All Grades 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

	EPKINLY + Lenalidomide and Rituximab ¹		Lenalidomide and Rituximab ¹	
Laboratory Abnormality	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Neutrophils decreased	88.1	69.1	78.0	44.9
Lymphocytes decreased	86.0	63.2	58.3	15.3
Hemoglobin decreased	67.5	8.6	51.9	4.6
Platelets decreased	51.9	11.5	40.3	6.4
Chemistry				
Alanine aminotransferase increased	58.8	7.0	39.1	0.9
Phosphate decreased ²	51.0	N/A	28.8	N/A
Sodium decreased	44.9	4.1	23.4	3.0
Potassium decreased	44.4	9.5	20.5	5.1
Aspartate aminotransferase increased	41.2	3.3	31.2	0.9
Laboratory abnormalities were graded based on CTCAE Version 5.0				
¹ The denominator used to calculate the rate varied from 241 to 243 in the EPKINLY arm, and 229 to 237 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).				

8.5. Post-Market Adverse Reactions

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

- haemophagocytic lymphohistiocytosis (HLH)
- progressive multifocal leukoencephalopathy (PML)

9. Drug Interactions

9.2. Drug Interactions Overview

No formal drug interaction studies have been conducted with EPKINLY.

9.3. Drug-Behaviour 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/ μ l) 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 , TNF α , 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_{0-7d} 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_{0-14d} 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_{0-28d} 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.

Epcoritamab in Combination with lenalidomide and rituximab

Based on populational pharmacokinetic modelling, there were no clinically meaningful differences in pharmacokinetic parameters when EPKINLY was administered in combination with lenalidomide and rituximab compared to EPKINLY administered as monotherapy.

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 ($CrCl \geq 30$ mL/min to $CrCl < 90$ mL/min), and mild hepatic impairment (total bilirubin $\leq$ 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.

10.4. 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]).

In EPCORE NHL-1 clinical study, 4 of 158 (2.5%) patients with DLBCL 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.

Anti-epcoritamab antibodies developed in 2.1% of patients (5 of 238) with FL treated with epcoritamab in combination with lenalidomide and rituximab in Study EPCORE FL-1 (up to 12 cycles) (see [14 Clinical Trials](#)).

Due to the low number of patients with ADAs, a meaningful analysis of the clinical and clinical pharmacology impact of ADA is limited.

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 2: 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 14. 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 relapsed or 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 15. 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).

Follicular lymphoma

Trial Design and Study Demographics

Table 16. Summary of Patient Demographics for Clinical Trials in Follicular Lymphoma (FL)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range) Years	Sex n (%)
EPCORE FL-1 (M20-638)	open-label, randomized, multicenter global trial	Patients were randomized to receive EPKINLY in combination with lenalidomide and rituximab (Epc + R²) or lenalidomide and rituximab alone (R²). <u>EPKINLY dosing:</u> • Cycle 1: ○ Day 1 – 0.16 mg ○ Day 8 – 0.8 mg ○ Day 15 – 3 mg ○ Day 22 – 48 mg • Cycles 2 - 3: EPKINLY 48 mg on Days 1, 8, 15, and 22 • Cycles 4 - 12: EPKINLY 48 mg on Days 1 Or until disease progression or unacceptable toxicity, which occurred first. In both treatment arms, lenalidomide was given orally at a dose of 20 mg once daily from Days 1 to 21 for 12 Cycles (For patients with CrCl < 60 mL/min at study entry, lenalidomide was started from 10 mg daily, going up to 15 mg if tolerated for 2 cycles) while rituximab was administered intravenously at a dose of 375 mg/m² on Days 1, 8, 15, and 22 of Cycle 1, followed by administration on Day 1 of Cycles 2 to 5.	Epc + R²: 243 R²: 245	Epc + R²: 59.5 (30 - 84) R²: 61.7 (24 - 89)	Epc + R²: Female 104 (43) Male 139 (57) R²: Female 107 (44) Male 138 (56)

Study EPCORE FL-1 was an open-label, randomized, multicenter, global clinical trial which evaluated EPKINLY in combination with lenalidomide and rituximab in patients with relapsed or refractory

follicular lymphoma (R/R FL) after at least one prior line of therapy containing an anti-CD20 monoclonal antibody drug in combination with chemotherapy. Patients were randomized to receive EPKINLY in combination with lenalidomide and rituximab (Epcor + R²) or lenalidomide and rituximab alone (R²). Eligible patients had histologically confirmed CD20+ Grade 1 to 3a FL. The study excluded patients with known CNS involvement by lymphoma, prior allograft, known active infection, known impaired T-cell immunity, creatinine clearance < 50 mL/min, alanine transaminase > 3 times the upper limit of normal, clinically significant cardiovascular disease, and lenalidomide-refractory disease.

Patient characteristics were generally balanced between the two groups. The median age of patients on study was 61 (range: 24 to 89), 57% were male, and most were either of White (73%) or Asian descent (24%) or Black or African American (2%).

Disease-related baseline characteristics in the Intent to treat population were as follows: Sixty nine percent of patients had eastern cooperative oncology group (ECOG) performance status 0. ECOG 1 was reported in 29% and ECOG 2 was reported in 2%. Ann Arbor stage II occurred in 17%, stage III occurred in 29%, and stage IV in 54%. Bulky disease (>6 cm) was present in 34%. Baseline follicular lymphoma international prognostic index (FLIPI) scores were 0 to 1 in 24%, FLIPI score of 2 was reported in 32%, and FLIPI score of 3 to 5 in 44%. The median number of prior therapies was 1 (range 1 to 7); 59% had one prior line, 24% had two prior lines, and 17% had three or more lines. Prior stem cell transplant was reported in 8%. Refractory to the last line of therapy was reported in 34%; refractory to both anti-CD20 and alkylator therapy was reported in 37%. Progression of disease within 24 months of first-line systemic therapy (POD24) was reported in 41%.

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

Study Results

Efficacy was established based on dual primary measures, which were progression free survival (PFS) and overall response rate (ORR) determined by Lugano 2014 criteria as assessed by Independent Review Committee (IRC). Additional efficacy outcome measures included complete response (CR) and duration of response (DOR). EPCORE FL-1 demonstrated a statistically significant improvement in both PFS and ORR by IRC assessment for EPKINLY in combination with lenalidomide and rituximab compared to lenalidomide and rituximab alone.

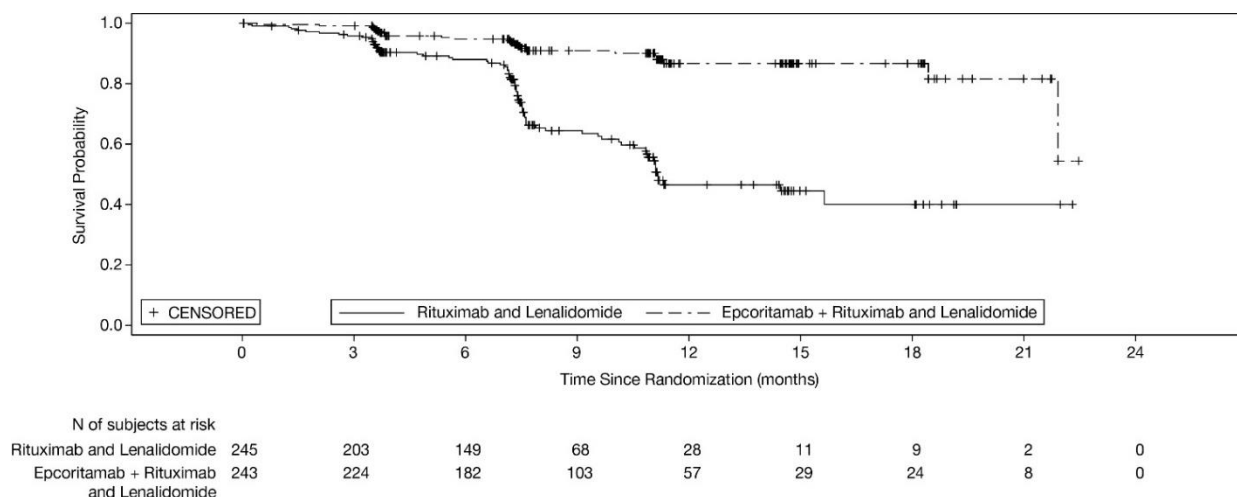
In the ITT population (data cut off date 10 January 2025), the median duration of study follow-up in patients who were randomized to receive EPKINLY in combination with lenalidomide and rituximab was 10.4 months (range: 0 to 27). The median duration of study follow-up in patients who were randomized to receive lenalidomide and rituximab alone was 10.2 months (range: 0 to 25).

Table 17. Efficacy Results in Study EPCORE FL-1

Outcome per IRC	EPKINLY +lenalidomide and rituximab (N = 243)	lenalidomide and rituximab (N=245)
Primary endpoints		
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 (95% CI) ^{b, e}	0.21 (0.13, 0.33)	
P-value ^{b, d}	< 0.0001	
ORR, n (%) ^c	111 (96)	94 (81)
(95% CI)	(90.2, 98.6)	(72.7, 87.7)
Risk difference (95% CI) ^{a, b}	14.9 (7.1, 22.8)	
P-value ^{b, f}	< 0.0001	
Key secondary endpoint		
CRR, n%	181 (74)	106 (43)
(95% CI)	(68.5, 79.8)	(37.0, 49.7)
Risk difference (95% CI) ^{a, b}	31.3 (23.1, 39.4)	
P-value ^{b, f}	< 0.0001	
PFS = progression free survival; NR = not reached; ORR = overall response rate; CRR= complete response rate. a. Based on Mantel-Haenszel method adjusted for randomization stratification factors b. Stratified by disease history and region c. Based on Lugano Criteria per IRC assessment in the first 232 patients from ITT population with at least 12 months (48 weeks) of follow-up from the date of randomization. d. P-value (one-sided) is by stratified log-rank test. e. HR is from stratified Cox proportional hazard model. f. P-value (one-sided) is by stratified Cochran-Mantel-Haenszel test.		

The Kaplan-Meier curve for PFS as determined by Lugano 2014 criterial per IRC assessment is shown in Figure 1.

Figure 1: Kaplan-Meier Plot of PFS (ITT Population) EPCORE FL-1



After a median duration of follow-up of 14.8 months, the median overall survival had not been reached in either arm.

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)

This patient medication information is written for the person who will be taking **EPKINLY**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This patient medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **EPKINLY**, talk to a healthcare professional.

Serious warnings and precautions box

- 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.
- Blurry vision, loss of vision or seeing two things when there is only one (double vision) may be symptoms of serious and potentially fatal brain condition called progressive multifocal leukoencephalopathy (PML). Other symptoms of PML are trouble speaking, feeling weak or clumsy in an arm or leg, changes in the way you walk or problems with your balance, changes in your personality, thinking or memory, which may lead to confusion.
- Fever (38°C or higher), low blood cell counts, bruising (dark mark on the skin) more easily, liver problems which may be symptoms of serious side effect called Haemophagocytic lymphohistiocytosis (HLH)

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 EPKINLY is 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.

For the following indication(s) EPKINLY has been approved without conditions. This means it has passed Health Canada's review and can be bought and sold in Canada.

- EPKINLY is used together with lenalidomide and rituximab to treat adult patients with follicular lymphoma (FL) that has come back or did not respond to previous treatment.

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 EPKINLY works:

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.

The ingredients in EPKINLY are:

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), immune effector cell associated neurotoxicity syndrome (ICANS), haemophagocytic lymphohistiocytosis (HLH) and progressive multifocal leukoencephalopathy (PML).

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

Haemophagocytic lymphohistiocytosis (HLH). Symptoms may include:

- fever
- low blood cell counts
- bruising (dark mark on the skin) more easily
- liver problems

Progressive multifocal leukoencephalopathy (PML). Symptoms of this serious and potentially fatal brain condition may include:

- blurry vision

- loss of vision or seeing 2 things when there's only 1 (double vision)
- trouble speaking
- feeling weak or clumsy in an arm or leg
- changes in the way you walk or problems with your balance
- changes in your personality, thinking, or memory, which may lead to confusion

These symptoms may start several months after treatment has ended. They usually develop slowly over weeks or months. It is important that your relatives or caregivers know of these symptoms, since they may notice some you are not aware of.

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.

Refer to the lenalidomide and the rituximab Product Monographs for additional information.

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.

For patients with relapsed or refractory diffuse large B-cell lymphoma

You will be given EPKINLY according to the following schedule:

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

For patients with relapsed or refractory follicular lymphoma

You will be given EPKINLY together with lenalidomide and rituximab according to the following schedule:

Cycle	EPKINLY Dosing Schedule
Cycle 1 to 3	Weekly
Cycles 4 to 12	Every four weeks

You will be given rituximab weekly during Cycle 1 and every four weeks during Cycles 2 to 5.

You will be given lenalidomide daily (on Days 1-21) during your treatment (Cycles 1 to 12).

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:**Diffuse large B-cell lymphoma**

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.

Follicular lymphoma

You will be given EPKINLY together with lenalidomide and rituximab, EPKINLY will be given in three small doses on Day 1 of Cycle 1 (0.16 mg) and Day 8 of Cycle 1 (0.8 mg) and Day 15 of Cycle 1 (3 mg) to manage potential side effects to this therapy.

The first full dose (48 mg) of EPKINLY will be given to you on Cycle 1 Day 22.

You will be given EPKINLY for up to 12 cycles, 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.

Lenalidomide 20 mg will be given orally once daily (from Day 1 to Day 21) in Cycles 1-12 and rituximab 375 mg/m² intravenously every week in Cycle 1 (on Days 1, 8, 15, and 22) and every 4 weeks in Cycles 2-5 (on Day 1). You may receive a lower dose of lenalidomide if you have kidney problems.

Overdose:

If you think you, or a person you are caring for, have taken too much EPKINLY, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or 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.

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.

EPKINLY used for the treatment of diffuse large B-cell lymphoma

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)
- fever due to infection when you have low levels of white blood cells (febrile neutropenia)
- tender swollen lymph nodes, chest pain, cough or difficulty breathing, pain at the site of the tumour (tumour flare)
- 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)

EPKINLY used in combination with lenalidomide and rituximab for follicular lymphoma:

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

- upper respiratory tract infections (infection of the airways)
- COVID-19
- lung infection (pneumonia)
- hypogammaglobulinemia is a condition in which the body does not produce enough antibodies to fight infections
- difficulties sleeping
- effects on your nervous system (neurological changes)
- headache

- diarrhea
- constipation
- nausea
- rash
- feeling tired (fatigue)
- injection site reactions
- fever
- an increase in liver tests, which show how your liver is working

Shown in blood tests:

- low levels of some white blood cells (neutropenia)
- 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, as measured in blood tests, of lymphocytes (a type of white blood cell; lymphopenia), that may affect the body's ability to fight infection
- low level of potassium in blood

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

- a viral infection that may cause symptoms such as fever, pain, redness, and/or difficulty breathing (cytomegalovirus infection)
- viral infection of the mouth or genitals (herpes virus infection)
- fever due to infection when you have low levels of white blood cells (febrile neutropenia), an inflammation of the mucous membranes, which are the moist lining of the digestive, respiratory and genitourinary systems

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 this 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,		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
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		√	
Uncommon			
Haemophagocytic lymphohistiocytosis (HLH): fever, low blood cell counts, bruising (dark mark on the skin) more easily, liver problems		√	
Progressive multifocal leukoencephalopathy (PML): Symptoms of this serious and potentially fatal brain condition may include blurry vision, loss of vision or seeing 2 things when there's only 1 (double vision), trouble speaking, feeling weak or clumsy in an arm or leg, changes in the way you walk or problems with your balance, changes in your personality, thinking, or memory, which may lead to confusion		√	

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 (canada.ca/drug-device-reporting) 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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