Drug Monograph

A - Drug Name

epcoritamab

COMMON TRADE NAME(S): Epkinly™

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B - Mechanism of Action and Pharmacokinetics

Epcoritamab is a humanized IgG1-bispecific, T-cell engaging antibody that binds to CD20 on B cells and to CD3 on T cells. Simultaneous engagement of CD20-expressing cells and CD3-expressing T cells induces T-cell activation, causes the release of proinflammatory cytokines, and results in lysis of CD20-expressing B cells.

Absorption	T max	4 days (after the first full dose in Cycle 1) 2.3 days (at the end of Cycle 3)
Distribution	Cross blood brain barrier?	Unknown
	PPB	Unknown
Metabolism	Expected to be degraded into small peptides and amino acids via catabolic pathways	
Elimination	Expected to undergo saturable target-mediated drug clearance.	
	Half-life	of full dose epcoritamab (48 mg): 22 - 25 days, based on frequency of dosing

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C - Indications and Status

Health Canada Approvals:

- Diffuse large B-cell lymphoma (DLBCL)
- High grade B-cell lymphoma (HGBCL)
- Primary mediastinal B-cell lymphoma (PMBCL)
- Follicular lymphoma

(Includes conditional approvals)

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Minimal

The adverse events in this table were reported in a Phase I/ II study that evaluated epcoritamab monotherapy in patients with relapsed or refractory large B-cell lymphoma (LBCL). The following adverse events were reported in ≥ 5% of patients treated with epcoritamab in this study; severe or life-threatening adverse events may also be included from other sources or post-marketing.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (12%) (including QT prolongation) (<1% severe)	E
	Arterial thromboembolism (rare)	E
	Hypotension (7%)	I E
	Venous thromboembolism (rare)	E
Dermatological	Rash, pruritus (15%)	E D
Gastrointestinal	Abdominal pain (23%)	E
	Anorexia (12%)	E
	Constipation (13%)	E
	Diarrhea (20%)	E
	Nausea, vomiting (20%) (1% severe)	E
General	Edema (14%)	E

	Fatigue (30%) (3% severe)	E
	Fever (24%)	I E
Hematological	Myelosuppression ± infection (28%) (21% severe)	E D
Hepatobiliary	↑ ALT (6%) (<1% severe)	E
	Hepatotoxicity (rare)	E
Immune	Cytokine release syndrome (50%) (3% severe)	I
	Other (3%) Hypogammaglobulinemia	E D
Injection site	Injection site reaction (28%)	I
Metabolic / Endocrine	Abnormal electrolyte(s) (8%) (↓K, ↓Mg, ↓PO4)	E
	Tumour lysis syndrome (1%)	E
Musculoskeletal	Musculoskeletal pain (10%)	E
Nervous System	Headache (13%)	E
	Immune effector cell-associated neurotoxicity syndrome (6%) (<1% severe)	I E
	Insomnia (10%)	E
Respiratory	Cough, dyspnea (7%)	E
	Pleural effusion (9%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for epcoritamab include cytokine release syndrome, fatigue, injection site reaction, myelosuppression ± infection, fever, abdominal pain, diarrhea, nausea, vomiting, rash, pruritus and edema.

Cytokine release syndrome (CRS) occurred in half of patients receiving epcoritamab. The majority of events were Grade 1 and occurred during Cycle 1. Most CRS events were associated with administration of the first full dose of epcoritamab (61% of CRS events occurred after the 48mg dose on Cycle 1, Day 15 in LBCL patients) and were much less frequent after the other doses during Cycle 1 (9% after Day 1, 16% after Day 8 and 6% after Day 22). Patients should be monitored closely for 24 hours following the administration of the first full dose (48mg). The most commonly reported CRS signs and symptoms were pyrexia, hypotension and hypoxia; others included chills, tachycardia, headache and dyspnea. The overall median time to onset was 2 days (range: 1 to 11 days); however, onset was shorter after the first full dose (median: 21 hours, range: 0.2 to 7 days). Most CRS events (98%) resolved with a median duration of 3 days (range: 1 to 27 days). Tocilizumab was used to manage CRS in 28% of patients in the clinical trial. Prophylactic pre-medications should be administerd and the step-up schedule should be followed in order to reduce

the risk of CRS.

Serious infections, including fatal infections, opportunistic infections, and viral reactivations, have occurred with epcoritamab. Infections were observed in 45% of LBCL patients and Grade 3 or 4 infections were reported in 15%, most commonly COVID-19 and sepsis. In patients with follicular lymphoma (FL), serious infections were reportedly higher, in 40% of patients. Similar to LBCL patients, the majority of fatal events in patients with FL were due to COVID-19 but also included pneumonia and sepsis. Prophylactic antimicrobials should be administered according to local guidelines.

Serious or life-threatening neurological events, or **Immune effector cell associated neurotoxicity syndrome (ICANS),** can manifest as altered level of consciousness, cognitive impairment, cerebral edema, aphasia, motor weakness or seizures. In patients with LBCL, ICANS occurred in 6% of patients, including one fatal case. The majority of ICANS events were Grade 1 (70%) and occurred during Cycle 1 (90%), however some had a delayed onset. Onset ranged from 8 to 141 days to an ICANS event from the start of treatment, with a median onset time of 16.5 days (after the first treatment dose). From the most recently administered dose, the median time to onset was 3 days (range: 1 to 13 days). ICANS generally lasted 5 days (median, range 1 to 9 days) and resolved in most patients (90%) with the use of supportive care. The onset of ICANS was irrespective of CRS (may occur concurrently, after, or in the absence of CRS).

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E - Dosing

Refer to protocol by which patient is being treated.

Do not start treatment with epcoritamab in patients with active infection.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Pre-medications (prophylaxis for CRS):

Cycle 1:

Give 30 -120 minutes before each epcoritamab dose during Cycle 1:

- Dexamethasone 15 mg PO/IV (or equivalent)
- Diphenhydramine 50 mg PO/IV (or equivalent)
- Acetaminophen 650-1000 mg PO

Give after each epcoritamab dose during Cycle 1:

- Dexamethasone 15 mg PO/IV (or equivalent) x 3 days

Cycle 2 and onwards (only for patients who experienced Grade 2 or 3 CRS with previous dose):

Give 30 -120 minutes before each epcoritamab dose*:

- Dexamethasone 15 mg PO/IV (or equivalent)

Give after each epcoritamab dose*:

- Dexamethasone 15 mg PO/IV (or equivalent) x 3 days

*Continue to give with subsequent doses until Grade ≥ 2 CRS does not occur.

Other Supportive care:

- Consider prophylaxis against Pneumocystis jirovecii pneumonia (PJP) and herpes virus infections.
- Consider other antimicrobial prophylaxis as per local guidelines.
- Epcoritamab should be administered to adequately hydrated patients.
- Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.

Adults:

Epcoritamab should be administered according to the step-up schedule below to reduce the risk of CRS.

Each cycle is 28 days

Cycle 1:

	Day of Treatment	**Epcoritamab Dose (mg, Subcut)**
Step-up dose 1	1	0.16
Step-up dose 2	8	0.8
First treatment dose	15	48
	22	48

Cycle 2 & 3:

Subcut: 48 mg on Days 1, 8, 15 and 22

Cycles 4 to 9:

Subcut: 48 mg on Days 1 and 15

Cycles 10 and onwards:

Subcut: 48 mg on Day 1

Note: Inpatient admission may be required for CRS monitoring. ST-QBP funding for ambulatory administration only.

Dosage with Toxicity:

Table 1 - CRS and ICANS Toxicity Management

Recommendations below are based on the pivotal trial. Refer to Crombie et al. for alternative CRS and ICANS management guidelines.

Toxicity	Grade[a]	Management / Action	Next dose
CRS	Grade 1	Hold until CRS has resolved. Manage and treat symptoms as appropriate[b]: • Consider corticosteroid (e.g. dexamethasone). • Consider anticytokine therapy (e.g. tocilizumab) in certain cases.	Resume dose as recommended in Table 3.
	Grade 2	Hold until CRS has resolved. Manage and treat symptoms as appropriate[b]: • Tocilizumab IV as per institutional guidelines.	Administer pre-treatment medications prior to next dose. Monitor patient more frequently following next dose; consider

		• Consider dexamethasone 10 - 20mg/ day (or equivalent). • If no improvement, initiate or increase dose of corticosteroid and consider alternative anticytokine therapy.	hospitalization. Resume dose as recommended in Table 3.
	Grade 3	Hold until CRS has resolved. Manage and treat symptoms as appropriate[b]: • Tocilizumab IV as per institutional guidelines • If no improvement, initiate or increase dose of corticosteroid and consider alternative anticytokine therapy. • Dexamethasone (e.g. 10 - 20mg IV q6h). If no response, initiate methylprednisolone IV 1000mg / day.	Administer pre-treatment medications prior to next dose. Hospitalize for monitoring after next dose. Resume dose as recommended in Table 3.
	Grade 4	Stop epcoritamab. Manage and treat symptoms as appropriate[b]: • Tocilizumab IV as per institutional guidelines • If no improvement, initiate or increase dose of corticosteroid and consider alternative anticytokine therapy. • Dexamethasone (e.g. 10 - 20mg IV q6h). If no response, initiate methylprednisolone IV 1000mg / day.	Permanently discontinue.
ICANS	Grade 1	Hold until ICANS has resolved. Manage and treat symptoms as appropriate[b]: • Dexamethasone IV 10mg q12h • Consider seizure prophylaxis (e.g. levetiracetam).	Resume dose as recommended in Table 3.
	Grade 2	Hold until ICANS has resolved. Manage and treat symptoms as	Resume dose as recommended in Table 3.

		appropriate[b]: • Dexamethasone IV 10 - 20 mg q12h • Consider seizure prophylaxis (e.g. levetiracetam).	
	Grade 3 (1st occurrence)	Hold until ICANS has resolved. Manage and treat symptoms as appropriate[b]: • Dexamethasone IV 10 - 20 mg q6h • If no response, initiate methylprednisolone IV 1000mg / day. • Consider seizure prophylaxis (e.g. levetiracetam).	Resume dose as recommended in Table 3.
	Grade 3 (recurrent), or Grade 4	Stop epcoritamab. Manage and treat symptoms as appropriate[b]: • Dexamethasone IV 10 - 20 mg q6h • If no response, initiate methylprednisolone IV 1000mg / day. • Consider seizure prophylaxis (e.g. levetiracetam).	Permanently discontinue.

[a] Grade based on American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading (Lee et al 2019).

[b] Anticytokine therapy is recommended if ICANS occurs concurrently with CRS. Refer to EPCORE NHL-1 study protocol, or local institutional guidelines for management of concurrent CRS and ICANS.

Table 2 - Hematologic and Other Non-hematologic Toxicities

Toxicity	Severity	Action
Active Infection	Grade 1 to 3	Hold* until infection fully resolves.
	Grade 4	Hold* until infection fully resolves, OR Consider discontinue.
Neutropenia	ANC < 0.5 × 10^9/L	Hold* until ANC ≥ 0.5 × 10^9/L.
Thrombocytopenia	Platelets < 50 × 10^9/L	Hold* until platelets ≥ 50 × 10^9/L.
Other adverse effects	Grade ≥ 3	Hold* until toxicity improves to Grade ≤ 1. Consider discontinue for events associated with severe outcomes.

*Resume at dose described in Table 3

Table 3 - Recommended Restarting Doses After Dose Delay

Last Administered Dose	Time since Last Dose	Action for Next Dose
Step-up Dose 1 (0.16 mg)	> 8 days	Repeat Cycle 1 schedule starting at Step-up Dose 1 (0.16 mg), then resume the planned treatment schedule.
Step-up Dose 2 (0.8 mg)	≤ 14 days	Resume at 48 mg and resume planned treatment schedule.
	> 14 days	Repeat Cycle 1 schedule starting at Step-up Dose 1 (0.16 mg), then resume the planned treatment schedule.
Any Treatment Dose (48 mg)	≤ 42 days	Resume at 48 mg and resume planned treatment schedule.
	> 42 days	Repeat Cycle 1 schedule starting at Step-up Dose 1 (0.16 mg), then resume the planned treatment schedule.

Dosage with Hepatic Impairment:

Severity	Bilirubin		AST	Epcoritamab Dose
Mild	≤ ULN	AND	> ULN	No dose adjustment
	> 1 to 1.5 x ULN	AND	any	No dose adjustment
Moderate or Severe	> 1.5 x ULN	AND	any	No data

Dosage with Renal Impairment:

Severity	Creatinine Clearance (mL/min)	Epcoritamab Dose
Mild or Moderate	≥ 30	No dose adjustment
Severe or ESRD	< 30	No data

Dosage in the elderly:

No clinically meaningful differences in safety or efficacy were observed between patients ≥ 65 years of age compared with younger patients. Approximately one third of LBCL patients in the EPCORE NHL-1 trial were ≥ 65 years of age and 18% were ≥ 75 years of age.

Dosage based on gender:

There were no clinically significant differences in the pharmacokinetics of epcoritamab based on sex.

Dosage based on ethnicity:

There were no clinically significant differences in the pharmacokinetics of epcoritamab based on race or ethnicity.

Dosage based on body weight:

Body weight had a statistically significant effect on the pharmacokinetics of epcoritamab. Average epcoritamab concentrations after the first full dose (48 mg) were 31% lower in patients with body weight 85 to 172 kg and 13% higher in patients with body weight 39 to 65 kg compared to patients with body weight of 65 to < 85 kg. However, this effect was not clinically relevant across body weight categories (< 65kg, 65 to < 85, ≥ 85).

Children:

The safety and efficacy of epcoritamab in pediatric patients (< 18 years of age) has not been established.

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F - Administration Guidelines

- Epcoritamab should be administered by **subcutaneous injection only.**
- Certain doses of epcoritamab may require dilution; refer to product monograph for details on preparation.
- To minimize injection pain, allow solution to come to room temperature (for no more than 1 hour) before administration.
- Inject into lower abdomen (preferred) or thigh. Change injection site (from left to right or vice versa), especially during weekly administration (Cycles 1 - 3).
- Do not inject into areas where skin is red, bruised, scarred, tattooed or not intact.
- Monitor patients after administration of all doses in Cycle 1 and for 24 hours after the first full dose (Cycle 1, Day 15) for signs and symptoms of CRS or ICANS.
- Store unopened vials refrigerated (2°C to 8°C) and protect from light.

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to this drug or to any of its components.

Other Warnings/Precautions:

- Serious and life-threatening CRS and ICANS have occurred with epcoritamab; ensure step-up schedule is followed and infusions are administered where there is immediate access to medications and equipment required to manage CRS and ICANS.
- Patients should avoid driving or operating heavy machinery if any new neurological symptoms present due to the risk of depressed level of consciousness from ICANS.
- Avoid administration of epcoritamab in patients with clinically significant active infections.
- Patients should not receive live or live-attenuated vaccines for at least 4 weeks prior to or during treatment with epcoritamab. The risk of vaccine-associated infection may be increased or immune response to vaccines may be reduced.
- Patients with high tumour burden or rapidly proliferative tumours, and patients with reduced renal function are at risk of tumour lysis syndrome.
- Patients with conditions such as LVEF < 45%, CNS involvement, allogenic HSCT or solid organ transplant, and impaired T-cell immunity were excluded from the clinical trial; assess benefit-risk of epcoritamab treatment in these patients.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Genotoxicity: Unknown
- Fetotoxicity: Probable
  May cause fetal harm, including B-cell lymphocytopenia and changes in normal immune responses, since IgG1 antibodies (such as epcoritamab) can cross placenta

- Pregnancy:
  Epcoritamab is **not recommended** for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **4 months** after the last dose.

- Breastfeeding:
  Breastfeeding is **not recommended** during treatment and for at least **4 months** after the last dose.
- Excretion into breast milk: Probable
  Unknown whether epcoritamab is excreted in human milk, but IgGs are known to be present in milk, therefore neonatal exposure to epcoritamab may occur through lactation.

- Fertility effects: Unknown

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H - Interactions

Epcoritamab causes a transient release of cytokines that may suppress CYP450 enzymes, resulting in an increased exposure to CYP substrates. Transient elevations of cytokines occurred, mostly after the first full dose (48 mg), with peak levels between 24 and 72 hours. Monitor patients receiving concomitant CYP450 substrates, especially those that have a narrow therapeutic index, for increased substrate concentrations or toxicity.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP 2C9 substrates (e.g. warfarin, meloxicam, fluvastatin)	↑ substrate concentration and/or toxicity	cytokines may suppress CYP450	Monitor and adjust dose of substrates with narrow therapeutic index (e.g. warfarin) if necessary
CYP3A4 substrates (e.g. cyclosporine, pimozide, tacrolimus, triazolo-benzodiazepines, dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors)	↑ substrate concentration and/or toxicity	cytokines may suppress CYP450	Monitor and adjust dose of substrates with narrow therapeutic index (e.g. cyclosporine) if necessary

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and before each dose; more frequently if clinically indicated
Clinical toxicity assessment for CRS and ICANS	At each visit and for 24 hours after the first treatment dose (Cycle 1, Day 15)
Renal function tests	Baseline and as clinically indicated
Liver function tests	Baseline and as clinically indicated
CRP, ferritin, coagulation tests (e.g. aPTT, INR, PT, fibrinogen)	Baseline and as clinically indicated
Electrolytes (e.g. K, Mg and PO4), uric acid levels	Baseline and as clinically indicated, especially for patients at risk of TLS
Clinical toxicity assessment for infection, injection-site reactions, TLS, pulmonary and cardiac toxicity.	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

High Cost Therapy Funding Program

- Epcoritamab (Inpatient) - Relapsed or Refractory Diffuse Large B-Cell Lymphoma

New Drug Funding Program (NDFP Website)

- Epcoritamab (Outpatient) - Relapsed or Refractory Diffuse Large B-Cell Lymphoma

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K - References

Canada's Drug and Health Technology Agency. CADTH Reimbursement Recommendation Epcoritamab (Epkinly). Canadian Journal of Health Technologies. June 2024; 4 (6).

Crombie JL, Graff T, Falchi L, et al. Consensus recommendations on the management of toxicity associated with CD3×CD20 bispecific antibody therapy. *Blood* 2024; 143 (16): 1565–1575.

Epcoritamab: Drug information. Waltham, MA: Lexi-Comp Inc., 2024. https://online.lexi.com. Accessed June 18, 2024.

Epcoritamab EU Product information. AbbVie Deutschland GmbH & Co. KG; May 2023.

Epkinly (epcoritamab-bysp) injection Full Prescribing Information. Genmab US, Inc. Plainsboro, New Jersey, USA; June 2024.

Epkinly epcoritamab injection Product Monograph. AbbVie Corporation. St-Laurent, Quebec; April 2024.

Lee W, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release Syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25:625-38.

NCCN Practice Guidelines in Oncology (NCCN Guidelines) - Antiemesis v.1.2024. NCCN, Dec 2023. Accessed April 22, 2024.

Protocol for: Thieblemont C, Phillips T, Ghesquieres H, et al. Epcoritamab, a novel, subcutaneous CD3xCD20 Bispecific T-Cell-Engaging antibody, in relapsed or refractory large B-cell lymphoma: dose expansion in a phase I/II Trial. J Clin Oncol 2023 Apr 20;41(12):2238-47.

Supplement to: Thieblemont C, Phillips T, Ghesquieres H, et al. Epcoritamab, a novel, subcutaneous CD3xCD20 Bispecific T-Cell-Engaging antibody, in relapsed or refractory large B-cell lymphoma: dose expansion in a phase I/II Trial. J Clin Oncol 2023 Apr 20;41(12):2238-47.

Thieblemont C, Phillips T, Ghesquieres H, et al. Epcoritamab, a novel, subcutaneous CD3xCD20 Bispecific T-Cell-Engaging antibody, in relapsed or refractory large B-cell lymphoma: dose expansion in a phase I/II Trial. J Clin Oncol 2023 Apr 20;41(12):2238-47.

November 2024 Updated units in Dosage with Renal Impairment section

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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