DRUG NAME: Epcoritamab

SYNONYM(S): GEN3013[1]; epcoritamab-bysp[2]

COMMON TRADE NAME(S): EPKINLY®

CLASSIFICATION: immunotherapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Epcoritamab is a humanized immunoglobulin G1 (IgG1) manufactured in Chinese hamster ovary cells. It is a T-cell engaging bispecific antibody that binds to the T-cell antigen CD3 and the B-cell antigen CD20 on malignant cells. By co-engaging CD3 and CD20, epcoritamab induces the activation of T cells which then causes the release of proinflammatory cytokines and the subsequent lysis of CD20 expressing B cells and tumour cells.[2-4]

PHARMACOKINETICS:

Absorption	T_{max} after first full dose (48 mg) in cycle 1 = 4 days; T_{max} after cycle 3 = 2.3 days	
Distribution	geometric mean central volume of distribution = 8.27 L	
	cross blood brain barrier?	no information found
	volume of distribution	25.6 L (at steady-state)
	plasma protein binding	no information found
Metabolism	expected to be degraded into small peptides and amino acids via catabolic pathways	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	expected to undergo saturable target mediated clearance	
	urine	no information found
	feces	no information found
	terminal half life	22-25 d
	clearance	0.53 L/day
Sex	no clinically significant difference	
Elderly	no clinically significant difference	
Ethnicity	no clinically significant difference	

Adapted from standard reference[1,2,4,5] unless specified otherwise.

USES:

Primary uses:

*Lymphoma, B-cell

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:
- severe ***cytokine release syndrome (CRS)*** can occur with epcoritamab; recommended dosing regimen uses a step-up dosing schedule for initiation of treatment[2,4]
- ***premedication*** is required before each dose in cycle 1 and for patients who experience any grade 2 or 3 CRS with a previous dose[2,4]
- epcoritamab should not be administered to patients with ***active infection***; consider ***antimicrobial/antiviral prophylaxis*** for *Pneumocystis jirovecii pneumonia* and herpes virus in high-risk patients[2,4]
- ***immunization with live or live-attenuated virus vaccines*** is not recommended for at least 4 weeks prior to treatment and during treatment with epcoritamab[2,4]
- patients should be ***adequately hydrated*** prior to starting treatment[2,4]
- patients may experience ***reduced consciousness*** due to CRS and immune effector cell-associated neurotoxicity syndrome (ICANS); ***driving or operating heavy machinery*** should be avoided until symptoms resolve[4]
- risk of ***tumour lysis syndrome*** is increased in patients with a high tumour burden, rapidly growing tumour, renal dysfunction, or dehydration

Carcinogenicity: No studies have been conducted.

Mutagenicity: No studies have been conducted.

Fertility: No studies have been conducted.

Pregnancy: Epcoritamab has not been studied in pregnant women. Epcoritamab causes T-cell activation and cytokine release which may compromise pregnancy maintenance. Human IgG is also known to cross the placental barrier and therefore, epcoritamab has the potential to be transmitted from mother to fetus. As epcoritamab is associated with B-cell depletion, infants exposed to epcoritamab in utero may develop B-cell lymphocytopenia and have altered immune responses. In females of childbearing potential, pregnancy tests are recommended prior to starting treatment and contraception is recommended during treatment and for four months after the last dose.[2,4]

Breastfeeding is not recommended due to the potential secretion into breast milk. Human IgG is known to be secreted in breast milk. Because of the potential for serious adverse reactions in breastfed infants, women should not breastfeed during treatment and for four months after the last dose.[2,4]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important[6,7].

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (19%, severe 10-12%)
	febrile neutropenia (severe 3%)
	leukopenia (3%)
	lymphopenia (5%)
	neutropenia (29%, severe 22%)
	thrombocytopenia (15%, severe 7-12%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
cardiac	***arrhythmias*** (12%, severe <1%); includes bradycardia, tachycardia, supraventricular extrasystole
	myocardial infarction (1%); fatal events reported
gastrointestinal	*emetogenic potential:* low[8]
	abdominal pain (23%, severe 2%)
	constipation (13%)
	diarrhea (20%)
	nausea (20%, severe 1%)
	vomiting (12%, severe <1%)
general disorders and administration site conditions	chills (5%)
	edema (14%, severe 2%)
	fatigue (29-30%, severe 3%)
	injection site reactions (27-28%)
	pain (5%)
	pyrexia (24%)
hepatobiliary	***hepatotoxicity*** (1%); fatal events reported
immune system	***cytokine release syndrome*** (50-51%, severe 3%); see paragraph following **Side Effects** table
	hypogammaglobulinemia (3%)
infections and infestations	COVID-19 (1%); fatal events reported
	infection, including bacterial, viral, and fungal infections (42%, severe 11-15%)
	pneumonia, including COVID-19 pneumonia (8%, severe 3%)
	sepsis (5%)
investigations	***ALT increase*** (45%, severe 5%)
	AST increase (48%, severe 5%)
	creatinine increase (24%, severe 3%)
	potassium increase (21%, severe 1%)
	sodium decrease (56%, severe 3%)
metabolism and nutrition	appetite decrease (12%, severe <1%)
	hypokalemia (8%, severe <1%)
	hypomagnesaemia (6%)
	hypophosphatemia (5%, severe 1%)
	tumour lysis syndrome (1%)
musculoskeletal and connective tissue	musculoskeletal pain (28%, severe 1%)
	arthralgia (7%, severe <1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	back pain (10%, severe <1%)
nervous system	headache (13%, severe <1%)
	immune effector cell-associated neurotoxicity syndrome (6%, severe <1%); see paragraph following **Side Effects** table
neoplasms	tumour flare (3%)
psychiatric	insomnia (10%, severe <1%)
respiratory, thoracic and mediastinal	cough (7%)
	dyspnea (7%, severe 2%)
	pleural effusion (9%, severe 4%)
	pulmonary embolism (1%); fatal events reported
skin and subcutaneous tissue	rash (15%, severe <1%)
	pruritus (7%)
vascular	hypotension (7%, severe 2%)

Adapted from standard reference[1,2,4,9] unless specified otherwise.

Cytokine release syndrome (CRS) is reported in approximately 50% of patients, with the majority of patients experiencing grade 1 or 2 reactions. Serious or life-threatening reactions can occur. Reported signs and symptoms include pyrexia, hypotension, hypoxia, dyspnea, chills, and tachycardia. Concurrent neurological reactions associated with CRS include headache, confusion, tremors, dizziness, and ataxia. Most events occur during the first cycle, and the majority of those occur after the first full dose on day 15. Median time to onset after the first full dose is 21 hours (range 0.2 to 7 days). CRS resolves in 98% of patients and the median duration of CRS events is 3 days (range 1 to 27 days). Recurrent CRS is reported in 16% of patients. To reduce the incidence and severity of CRS, epcoritamab treatment is initiated in a step-up dosing regimen. Premedicate with corticosteroid, antihistamine, and acetaminophen prior to each dose in the first cycle. Patients experiencing grade 2 or higher CRS with a previous dose should be premedicated with corticosteroids for subsequent cycles. If CRS is suspected, withhold epcoritamab until symptoms resolve and manage according to severity. Patients experiencing signs and symptoms of CRS should refrain from driving or operating machinery until symptoms have resolved. Permanently discontinue epcoritamab for grade 4 reactions.[2,4] For management of cytokine release syndrome (CRS), see BC Cancer Protocol SCCRS ***Cytokine Release Syndrome Management***.

Immune effector cell-associated neurotoxicity syndrome (ICANS) is reported in 6% of patients. The majority of patients experience grade 1 or 2 events, however life-threatening or fatal events can occur. Signs and symptoms of ICANS include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema. The majority of ICANS events occur during cycle 1, with a median time to onset of 17 days (range 8 to 141 days). The median duration is 5 days (range 1 to 9 days). ICANS can occur concurrently with CRS, following the resolution of CRS, or in the absence of CRS. Patients should be advised to report symptoms immediately if they occur. Withhold epcoritamab at the first signs of neurotoxicity. Neurology consult may be required. Management of ICANS may include anti-seizure medications for seizure prophylaxis and corticosteroids for symptom management. Provide supportive care as required. Withhold epcoritamab until ICANS resolves and permanently discontinue epcoritamab for grade 4 reactions and recurrent grade 3 reactions. Patients experiencing signs and symptoms of ICANS should refrain from driving or operating machinery until symptoms have resolved.[2,4] For inpatient management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) associated with cytokine release syndrome (CRS), see BC Cancer Protocol SCICANS ***Immune Effector Cell-Associated Neurotoxicity Syndrome Management.***

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INTERACTIONS:

Epcoritamab causes release of cytokines that may suppress the activity of CYP enzymes, resulting in increased exposure of CYP substrates. Substrates of CYP450 enzymes with a narrow therapeutic index may require dose adjustment and monitoring for toxicity if given concurrently with epcoritamab. Interactions with CYP substrates are most likely to occur after the first dose of epcoritamab (Cycle 1, day 1) and up to 14 days after the first full dose (Cycle 1, day 15), as well as during/after a CRS event.[2,4]

SUPPLY AND STORAGE:

***Injection*:**

AbbVie Corporation supplies epcoritamab as a single dose (preservative free) vial in two vial sizes: 4 mg vials in a concentration of 5 mg/mL and 48 mg vials in a concentration of 60 mg/mL. Non-medicinal ingredient: sorbitol (provides 25-30 mg/mL); clinical significance is unknown.[10] Refrigerate. Keep in original carton to protect from light. Do not shake.[4]

Additional information:

- ***Caution:*** epcoritamab vials are supplied as ***two different concentrations*** (5 mg/mL and 60 mg/mL); ensure selection of appropriate vial size for dose preparation[4]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:

- ***Caution:*** epcoritamab vials are supplied as ***two different concentrations***; ensure selection of appropriate vial size for dose preparation[4]
- 4 mg vials must be further diluted prior to use for step-up dose[4]
- do not use if discoloration or particulates are present[4]
- do not closed system transfer devices (CSTDs) for volumes less than 1 mL[11]
- for prepared solutions: minimize exposure to daylight and protect from light during periods of refrigerated storage prior to use[4]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous[2,4]	injection into the lower abdomen is preferred (may be administered into the thigh); alternate injections sites with each injection
Intramuscular	do NOT use
Direct intravenous	do NOT use
Intermittent infusion	do NOT use
Continuous infusion	do NOT use
Intraperitoneal	do NOT use
Intrapleural	do NOT use
Intrathecal	do NOT use

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BC Cancer administration guideline noted in ***bold***, ***italics***

Intra-arterial	do NOT use
Intravesical	do NOT use

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

Subcutaneous:

Cycle Length: 4 weeks[4,9]:

Cycle 1:

Dosing Schedule		Day of treatment	Dose (SC)
Step-up dosing schedule	Step-up dose 1	1	0.16 mg
	Step-up dose 2	8	0.8 mg
	First full treatment dose	15	48 mg
	Second full treatment dose	22	48 mg

(total dose per cycle 96.96 mg)

Cycles 2 and 3:
48 mg SC given once weekly on days 1, 8, 15, and 22
(total dose per cycle 192 mg)

Cycles 4 to 9:
48 mg SC given once on days 1 and 15
(total dose per cycle 96 mg)

Cycles 10 and beyond:
48 mg SC given once on day 1
(total dose per cycle 48 mg)

Following dose delays: for instruction about restarting epcoritamab, refer to protocol by which patient is being treated as the step-up regimen may need to be repeated[4]

Concurrent radiation: no information found

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Dosage in myelosuppression:	modify according to protocol by which patient is being treated
Dosage in renal failure:	CrCl ≥ 30 mL/min: no adjustment required[4] CrCl < 30 mL/min: no information found calculated creatinine clearance = N* x (140 - Age) x weight in kg / serum creatinine in micromol/L * For males N=1.23; for females N=1.04
Dosage in hepatic failure:	mild impairment (bilirubin ≤ 1.5 x ULN): no adjustment required[4] moderate/severe impairment: no information found
Dosage in dialysis:	no information found
Children:	safety and efficacy have not been established[4]

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