Epcoritamab Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
As monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy	C83	00896a	N/A

* This applies to post 2012 indications

TREATMENT:

Epcoritamab is administered by subcutaneous injection according to a step-up dosing schedule, to reduce the risk of cytokine release syndrome (CRS). If a dose is missed or delayed, see repriming rules as per Table 3. The full recommended dose is 48 mg, administered weekly (cycles 1 to 3); every two weeks (cycles 4 to 9) and every four weeks (from cycle 10 onwards). Each cycle is 28 days, and treatment is continued until disease progression or unacceptable toxicity whichever occurs first.
The recommended dosing schedule (including dose titration) is shown in Tables 1 and 2 below.

Reassessment of ongoing benefit versus cumulative toxicity is recommended after 12 months of therapy, particularly in patients in sustained complete response (CR). Treatment discontinuation at this point may be considered in select patients who have achieved a complete molecular remission (CMR), based on clinical experience and expert opinion; however, this approach is not yet supported by published data.

Due to the risk of cytokine release syndrome (CRS) and/or immune effector cell-associated neurotoxicity syndrome (ICANS), patients with DLBCL should be hospitalised for 24 hours after administration of the Cycle 1 Day 15 dose of 48 mg to monitor for signs and symptoms of toxicities.
In the event of CRS and/or ICANS, tocilizumab[i] and emergency equipment must be available for each patient. The treatment centre must have access to additional doses of tocilizumab[i] within 8 hours.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Table 1: Cycle 1 Step Up Treatment Schedule (4 doses)

Drug	Day	Dose	Route	Cycle Frequency
Epcoritamab[a]	1	0.16mg (Step up dose 1)	SC[b]	28 days
	8	0.8mg (Step up dose 2)		
	15	48mg (First full dose)		
	22	48mg		
[a]See Table 3 for recommendations on restarting epcoritamab after dose delays.				
[b]Administer via subcutaneous injection into lower abdomen or thigh. Alternate injection sites.				

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Table 2: Treatment schedule (cycle 2 onwards)

Drug	Cycle	Day	Dose	Route	Cycle Frequency
Epcoritamab[a]	2-3 (8 doses)	1, 8, 15, 22	48mg	SC[b]	Every 28 days
	4-9 (12 doses)	1, 15	48mg		
	10 onwards (1 dose per cycle)	1	48mg		
[a]See Table 3 for recommendations on restarting epcoritamab after dose delays.					
[b]Administer via subcutaneous injection into lower abdomen or thigh. Alternate injection sites.					

ELIGIBILITY:

- Indications as above
- ECOG 0-2

CAUTIONS:

- Any clinically significant active infection requiring therapy.
- Immunisation with live or live-attenuated virus vaccines is not recommended during treatment with epcoritamab.

EXCLUSIONS:

- Hypersensitivity to epcoritamab or any of the excipients
- Pregnancy and women of childbearing potential not using contraception
- Breastfeeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal, liver and bone profile
- Assess for tumour lysis syndrome (calcium, magnesium and phosphate)
- Blood glucose
- Immunoglobulin
- LDH
- ECG
- Virology screen* - Serology for Hepatitis B virus (HBV) [HBV sAg, HBV sAb, HBV cAb], Hepatitis C virus (HCV), human immunodeficiency virus (HIV), cytomegalovirus (CMV) [IgG] and Epstein–Barr virus (EBV)
- Pregnancy test

*See Regimen Specific Complications

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Regular tests:

- FBC, renal, liver and bone profile
- Assess for tumour lysis syndrome (calcium, magnesium and phosphate) in cycle 1 or as clinically indicated
- Blood glucose as clinically indicated
- Immunoglobulin every 6 months or sooner if clinically indicated
- LDH
- ECG as clinically indicated
- Patients should continue to be monitored for signs and symptoms of CRS and ICANS (refer to Tables 6 and 7 for management of CRS and ICANS)*
  *See Regimen Specific Complications

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Dose reductions of epcoritamab are not recommended.
- Dose delays may be required to manage toxicities related to epcoritamab. Recommendations for restarting treatment after a dose delay are outlined in Table 3.
- Any dose modification should be discussed with a Consultant.

Table 3: Recommendations for restarting therapy with epcoritamab after dose delay

Last dose administered	Duration of delay	Action
Step up dose 1 = 0.16 mg	> 8 days	• Restart dose titration schedule at step up dose 1 (0.16mg) [a] • After completing the step-up dosing schedule as per cycle 1, resume treatment with Day 1 of the next planned treatment cycle (subsequent to the cycle during which the dose was delayed).
Step up dose 2 = 0.8mg	> 14 days	
Any full dose = 48mg	> 6 weeks	

[a]Administer pre-treatment medicines as per cycle 1 and monitor patients accordingly.

Haematological:

Table 4: Dose modification in haematological toxicity

Haematologic toxicity	Recommended action
Absolute neutrophil count <0.5 x10^9/L	Withhold epcoritamab until absolute neutrophil count is ≥0.5 x10^9/L
Febrile neutropenia	Withhold epcoritamab until absolute neutrophil count is ≥0.5x10^9/L, and fever resolves.
Platelet count <50 x10^9/L	Withhold epcoritamab until platelet count is ≥50 x10^9/L

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Renal and Hepatic Impairment:

Table 5: Dose modification in renal and hepatic impairment

Renal Impairment	Hepatic Impairment
No dosage adjustment is recommended for patients with mild or moderate renal impairment. No data available in patients with severe renal impairment to end stage renal disease.	No dosage adjustment is recommended for patients with mild hepatic impairment. Limited data available for patients with moderate hepatic impairment. No data available in patients with severe hepatic impairment.
Renal and hepatic: Epcoritamab SPC	

Management of adverse events:

Cytokine release syndrome (CRS)

Patients treated with epcoritamab may develop cyctokine release syndrome (CRS). If CRS is suspected, manage according to the recommendations in Table 6. Patients who experience CRS should be monitored more frequently during next scheduled epcoritamab administration.

Table 6: CRS grading and management guidance

Grade[a]	Recommended therapy	Epcoritamab dose modification
Grade 1 • Fever (temperature ≥ 38 °C)	Provide supportive care such as antipyretics and intravenous hydration. dexAMETHasone[b] may be initiated. In cases of advanced age, high tumour burden, circulating tumour cells, fever refractory to antipyretics: • Anti-cytokine therapy, tocilizumab[i,d], should be considered. For CRS with concurrent ICANs refer to Table 7	Hold epcoritamab until resolution of CRS event
Grade 2 • Fever (temperature ≥ 38 °C) and • Hypotension not requiring vasopressors and/or • Hypoxia requiring low flow oxygen[e] by nasal cannula or blow-by	Provide supportive care such as antipyretics and intravenous hydration. dexAMETHasone[b] should be considered. Anti-cytokine therapy, tocilizumab[i,d] is recommended. If CRS is refractory to dexAMETHasone and tocilizumab[i]: • Alternative immunosuppressants[g] and methylPREDNISolone 1000mg/day intravenously should be administered until clinical improvement. For CRS with concurrent ICANs refer to Table 7	Hold epcoritamab until resolution of CRS event
Grade 3 • Fever (temperature ≥ 38 °C) and • Hypotension requiring a vasopressor with or without vasopressin and/or	Provide supportive care such as antipyretics and intravenous hydration dexAMETHasone[c] should be administered. Anti-cytokine therapy, tocilizumab[i,d], is recommended If CRS is refractory to dexAMETHasone and tocilizumab[i]: • Alternative immunosuppressants and methylPREDNISolone 1000 mg/day intravenously should be administered until clinical improvement.	Hold epcoritamab until resolution of CRS event In the event of Grade 3 CRS lasting longer than 72 hours, epcoritamab should be discontinued If more than 2 separate events of Grade 3 CRS, even if each event

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• Hypoxia requiring high flow oxygen[f] by nasal cannula, facemask, non-rebreather mask, or venturi mask	For CRS with concurrent ICANs refer to Table 7	resolved to Grade 2 within 72 hours, epcoritamab should be discontinued
Grade 4 • Fever (temperature ≥ 38 °C) and • Hypotension requiring ≥ 2 vasopressors (excluding vasopressin) and/or • Hypoxia requiring positive pressure ventilation (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	Provide supportive care such as antipyretics and intravenous hydration. dexAMETHasone[c] should be administered. Anti-cytokine therapy, tocilizumab[i,d] is recommended If CRS is refractory to dexAMETHasone and tocilizumab[i]: • Alternative immunosuppressants[g] and methylPREDNISolone 1000 mg/day intravenously should be administered until clinical improvement For CRS with concurrent ICANS refer to Table 7	Permanently discontinue epcoritamab

[a]CRS graded according to American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria
[b]dexAMETHasone should be administered at 10-20 mg per day (or equivalent)
[c]dexAMETHasone should be administered at 10-20 mg intravenously every 6 hours
[d]Tocilizumab[i] 8 mg/kg intravenously over 1 hour (not to exceed 800 mg per dose). Repeat tocilizumab[i] after at least 8 hours as needed. Maximum of 2 doses in a 24-hour period
[e]Low-flow oxygen is defined as oxygen delivered at < 6L/minute
[f]High-flow oxygen is defined as oxygen delivered at ≥ 6L/minute
[g]Riegler L et al. (2019)

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Patients should be monitored for signs and symptoms of ICANS. Other causes if neurologic symptoms should be ruled out. If ICANS is suspected, manage according to the recommendations in Table 7.

Table 7: ICANS grading and management guidance

Grade[a]	Recommended therapy	Epcoritamab dose modification
Grade 1[b] ICE score[c] 7-9[b] <u>or</u> depressed level of consciousness[b]: awakens spontaneously	Treatment with dexAMETHasone[d] Consider non-sedating anti-seizure medicinal products (e.g., levETIRAcetam) until resolution of ICANS <u>No concurrent CRS:</u> • Anti-cytokine therapy not recommended <u>For ICANS with concurrent CRS:</u> • Treatment with dexAMETHasone[d] • Choose immunosuppressant alternatives[e] to tocilizumab[i], if possible	Hold epcoritamab until resolution of event
Grade 2b ICE score[c] 3-6 <u>or</u> depressed level of consciousness[b]: awakens to voice	Treatment with dexAMETHasone[f] Consider non-sedating anti-seizure medicinal products (e.g., levETIRAcetam) until resolution of ICANS <u>No concurrent CRS:</u> • Anti-cytokine therapy not recommended	Hold epcoritamab until resolution of event

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Grade[a]	Recommended therapy	Epcoritamab dose modification
	<u>For ICANS with concurrent CRS:</u> • Treatment with dexAMETHasone[d] • Choose immunosuppressant alternatives[e] to tocilizumab[i], if possible	
Grade 3[b] ICE score[c] 0-2 <u>or</u> depressed level of consciousness[b]: awakens only to tactile stimulus, <u>or</u> seizures[b], either: • any clinical seizure, focal or generalised that resolves rapidly, or • non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, <u>or</u> raised intracranial pressure: focal/local oedema[b] on neuroimaging[c]	Treatment with dexAMETHasone[g]. ➢ If no response, initiate methylPREDNISolone 1000 mg/day Consider non-sedating anti-seizure medicinal products (e.g.levETIRAcetam) until resolution of ICANS <u>No concurrent CRS:</u> • Anti-cytokine therapy not recommended <u>For ICANS with concurrent CRS:</u> • Treatment with dexAMETHasone ➢ If no response, initiate methylPREDNISolone 1000 mg/day • Choose immunosuppressant alternatives[e] to tocilizumab[i], if possible	Permanently discontinue epcoritamab
Grade 4[b] ICE score[c], [b] 0 <u>or</u> depressed level of consciousness[b] either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, <u>or</u> seizures[b], either: • life-threatening prolonged seizure (> 5 minutes), or • repetitive clinical or electrical seizures without return to baseline in between, <u>or</u> motor findings[b]:	Treatment with dexAMETHasone[g] ➢ If no response, initiate methylPREDNISolone 1000 mg/day Consider non-sedating anti-seizure medicinal products (e.g., levETIRAcetam) until resolution of ICANS <u>No concurrent CRS:</u> • Anti-cytokine therapy not recommended <u>For ICANS with concurrent CRS:</u> • Treatment with dexAMETHasone ➢ If no response, initiate methylPREDNISolone 1000 mg/day • Choose immunosuppressant alternatives[e] to tocilizumab[i], if possible	Permanently discontinue epcoritamab

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Grade[a]	Recommended therapy	Epcoritamab dose modification
• 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		

[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 backward from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points.
[d] dexAMETHasone should be administered at 10 mg intravenously every 12 hours
[e] Alternatives such as anakinra[ii] or siltuximab[ii] have been suggested (Riegler et al 2019)
[f] dexAMETHasone 10-20 mg intravenously every 12 hours
[g] dexAMETHasone 10-20 mg intravenously every 6 hours

Table 8: Recommended dose modifications for other adverse events following administration of epcoritamab

Adverse reactions	Grade	Actions
Infections	All Grades	• Withold epcoritamab in patients with active infection until the infection resolves. • For Grade 4, consider permanent discontinuation of epcoritamab.
Other adverse reactions[a]	Grade 3 or higher	• Withhold epcoritamab until adverse reaction resolves to Grade 1 or baseline.

[a] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting Available on the NCCP website

Epcoritamab: Minimal (**Refer to local policy).**

For information:
Within NCIS regimens, antiemetics have been standardised by the Medical Oncologists and Haemato-oncologists and information is available in the following documents:

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- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

PREMEDICATIONS:

- Pre-medication with corticosteroids, antihistamines and antipyretics must be administered prior to each dose of epcoritamab during dose titration to reduce the risk of cytokine release syndrome as suggested in Table 6.
- Premedication is also required prior to administration of subsequent doses of epcoritamab for the following patients:
  - Patients who require re-priming with step up doses as per cycle 1 due to dose delays (Table 3)
  - Patients who experienced Grade 2 or 3 CRS following the previous dose (Table 6)

Table 9: Recommended premedications prior to administration of epcoritamab

Cycle	Patient requiring pre-medication	Pre-medication	Administration
Cycle 1	All patients	• PrednisoLONE (100mg oral[b]) or equivalent[a]	• 30 minutes[c] prior to each weekly administration of epcoritamab **And** • for three consecutive days following each weekly administration of epcoritamab in Cycle 1
		• Chlorphenamine (10mg intravenous) • Paracetamol 1g oral	• 30 minutes[b] prior to each weekly administration of epcoritamab
Cycle 2 onwards	Patients who experienced Grade 2 or 3[d] CRS with previous dose	• PrednisoLONE (100mg oral[b]) or equivalent[a]	• 30 minutes[b] prior to next administration of epcoritamab after a Grade 2 or 3[a] CRS event. **And** • for three consecutive days following the next administration of epcoritamab Until epcoritamab is given without subsequent any grade of CRS
[a] Prednisolone is the preferred steroid based on clinical experience (noting that dexamethasone was the preferred corticosteroid for CRS prophylaxis in the GCT3013-01 Optimisation study).			
[b] May be given by intravenous route also.			
[c] May be given 30-120 minutes prior to administration of epcoritamab.			
[d] Patients will be permanently discontinued from epcoritamab after a Grade 4 CRS event.			

OTHER SUPPORTIVE CARE:

- Patients should be adequately hydrated prior to starting treatment **(Refer to local policy)**
  It is strongly recommended that all patients adhere to the following fluid guidelines during Cycle 1:
  - 2-3L of fluid intake during the 24 hours prior to each epcoritamab administration

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  - Administer 500 ml isotonic intravenous (IV) fluids on the day of epcoritamab prior to dose administration
  - 2-3L of fluid intake during the 24 hours following each epcoritamab administration.
- Consider holding antihypertensive medications for 24 hours prior to each weekly dose in cycle 1.
- PJP and HSV prophylaxis **(Refer to local policy)**
- Antiviral prophylaxis **(Refer to local policy)**
- Tumour lysis prophylaxis **(Refer to local policy)**
- GCSF prophylaxis **(Refer to local policy)**
- Antifungal prophylaxis **(Refer to local policy)**
- Proton pump inhibitor **(Refer to local policy)**
- Mouthcare **(Refer to local policy)**
- Women of childbearing potential should be advised to use effective contraception during treatment with epcoritamab and for at least 4 months after the last dose.

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.
- **Epcoritamab is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.**

REGIMEN SPECIFIC COMPLICATIONS

- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy (Refer to local infectious disease policy). These patients should be considered for assessment by hepatology.
- **CRS:** which may be life-threatening or fatal, occurred in patients receiving epcoritamab. The most common signs and symptoms of CRS include pyrexia, hypotension and hypoxia. Other signs and symptoms of CRS in more than two patients include chills, tachycardia, headache and dyspnoea. Most CRS events occurred in cycle 1 and were associated with the first full dose of epcoritamab. Administer prophylactic steroids, antihistamines and antipyretics to mitigate the risk of CRS (see Table 6). Patients should be monitored for signs and symptoms of CRS following epcoritamab administration and patients should be hospitalized for 24 hours after administration of the cycle 1 day 15 dose of 48mg. At the first signs or symptoms of CRS, treatment should be instituted of supportive care with tocilizumab[i] and/or corticosteroids as appropriate (see Table 6). Patients should be counselled on the signs and symptoms associated with CRS and patients should be instructed to contact their healthcare professional and seek immediate medical attention should signs or symptoms occur at any time. Management of CRS may require either temporary delay or discontinuation of epcoritamab based on the severity of CRS.
- **ICANS:** including a fatal event, have occurred in patients receiving epcoritamab. ICANS may manifest as aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral oedema. The majority of cases of ICANS occurred within cycle 1 of epcoritamab treatment, however some occurred with delayed onset. Patients should be monitored for signs and symptoms of ICANS following epcoritamab administration and patients should be hospitalised for 24 hours after administration of the cycle 1 day 15 dose of 48mg. At the first signs or symptoms of ICANS, treatment with corticosteroids and non-sedating anti-seizure medicinal products should be instituted as appropriate (see Table 7). Patients should be counselled on the signs and symptoms of ICANS and

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that the onset of events may be delayed. Patients should be instructed to contact their healthcare professional and seek immediate medication attention should signs or symptoms occur at any time. Epcoritamab should be delayed or discontinued as recommended (see Table 7).

- **Haemophagocytic lymphohistiocytosis:** Haemophagocytic lymphohistiocytosis (HLH), including fatal cases, have been reported in patients receiving epcoritamab. HLH is a life-threatening syndrome characterized by fever, skin rash, lymphadenopathy, hepato- and/or splenomegaly and cytopenias. HLH should be considered when the presentation of CRS is atypical or prolonged. Patients should be monitored for clinical signs and symptoms of HLH. For suspected HLH, epcoritamab must be interrupted for diagnostic workup and treatment for HLH initiated.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

Patient card: https://assets.hpra.ie/products/Human/39929/2a69d979-4a87-48db-a4ae-da68e24c9cad.pdf

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Version	Date	Amendment	Approved By
1	29/07/2025		Dr. Liam Smyth

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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[i] This is an unlicensed indication for the use of tocilizumab in Ireland. Patients should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy

[ii] This is an unlicensed indication for the use of anakinra / siltuximab in Ireland. Patients should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy

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