Indication	Monotherapy for the treatment of previously treated diffuse large B-cell lymphoma (DLBCL) or transformed follicular lymphoma to DLBCL following 2 or more lines of systemic therapy, which included treatment with an anti-CD20 regimen, an anthracycline-containing regimen and polatuzumab vedotin unless the use of polatuzumab vedotin was contraindicated. No previous treatment with a bispecific antibody targeting both CD20 and CD3 is permitted unless epcoritamab monotherapy needs to be continued following an Abbvie compassionate access scheme or the patient received and responded to no more than three 4-weekly cycles of epcoritamab monotherapy used specifically as bridging treatment prior to 3rd or more line of CAR T therapy. NB: Primary CNS lymphoma, Burkitt lymphoma and plasmablastic lymphoma are NOT included for treatment with epcoritamab.
Treatment Intent	Disease Modification
Frequency and number of cycles	Repeat every 28 days Continue until disease progression, unacceptable toxicity or patient's choice to stop treatment. NB Once epcoritamab is electively stopped (i.e. not for reasons of toxicity), it cannot be restarted. A formal medical review as to whether treatment with epcoritamab should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Monitor FBC, U&Es and LFTs on: o Day 1, 8, 15 and 22 of cycles 1 to 3. o Day 1 and 15 of cycles 4 to 9 o Day 1 from cycle 10 onwards. • **Haematological parameters:** • If PLT <50x10^9/L withhold until PLT >/=50 x 10^9/l • Febrile neutropenia: ANC <0.5 x 10^9/L withhold until >/= 0.5 x 10^9/L • **Hepatic impairment:** The safety and efficacy of epcoritamab in patients with impaired hepatic function has not been established. No specific dose recommendations can be made, based on population pharmacokinetic (PK) analyses, no dosage adjustment is necessary for patients with mild hepatic impairment. No data are available in patients with moderate or severe hepatic impairment. • **Renal impairment:** The safety and efficacy of epcoritamab in patients with impaired renal function has not been established. No specific dose recommendations can be made, based on population pharmacokinetic (PK) analyses, no dosage adjustment is necessary for patients with mild or moderate renal impairment. No data are available in patients with severe renal impairment. • All patients should be adequately hydrated during treatment, consider IV hydration for those who cannot maintain an adequate level of oral hydration. • **Management of adverse reactions and dose adjustments:** o Healthcare professionals prescribing and administering epcoritamab must be familiar with the grading of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, the required monitoring and management and the indications for use of tocilizumab and have all undergone training in these clinical issues. • **Cytokine release syndrome (CRS).** o Patients must be admitted overnight for at least the **cycle 1 day 15** administration of epcoritamab and potentially for further epcoritamab administrations if grade 2 or greater cytokine release syndrome occurs with the previous epcoritamab injection.

	○ At least 1 dose of tocilizumab, at a dose of 8mg/kg IV (dose not to exceed 800 mg), for use in the event of CRS must be available prior to epcoritamab administration, access to an additional dose of tocilizumab within 8 hours of use of the previous tocilizumab dose must be ensured. ○ See **table 1 for** CRS dose modification and management guidance. ○ All patients must be counselled on the risk, signs and symptoms of CRS and advised to contact their healthcare team immediately if they experience signs and symptoms of CRS. • **Immune effector cell-associated neurotoxicity syndrome (ICANS):** ○ 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. ○ Patients 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 ICANS. See **table 2** for ICANS dose modification and management guidance. ○ All patients must be counselled on the risk, signs and symptoms of ICANS and advised to contact their healthcare team immediately if they experience signs and symptoms of ICANS. • **Tumour lysis syndrome (TLS) has been reported in patients receiving epcoritamab.** ○ Patients with a high tumour burden and/or a high circulating lymphocyte count (>25 x 10^9/L) and/or renal impairment (CrCl <70 mL/min) are considered at risk of TLS and should receive prophylaxis prior to treatment. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g. allopurinol), starting 12-24hours prior to subcutaneous administration**.** • **Tumour flare** has been reported in patients, monitoring and evaluation for tumour flare is recommended. • **Serious Infections:** Epcoritamab should be withheld for grade 1-4 infections. Use with caution in patients with a history of reoccurring or chronic infection, patients with underlying conditions that may pre-dispose them to infection or who have received significant prior immunosuppressive treatment. • **For all other grade 3 or higher adverse reactions** (excluding ICANS/CRS/infection) treatment should be withheld until toxicity resolves to Grade 1 or baseline. • **Common drug interactions (for comprehensive list refer to BNF/SPC):** ○ No formal drug interaction studies have been performed for epcoritamab. Due to the cytokine release at the start of treatment concomitant use with CYP450 substrates may lead to fluctuations in concentration, patient receiving substrates with a narrow therapeutic range (e.g. warfarin, cyclosporin) should be monitored closely. ○ Patients should not receive live vaccines during treatment. • **Missed dose:** A re-priming cycle (identical to Cycle 1 with standard CRS prophylaxis) is required: ○ If there are more than 8 days between the priming dose (0.16mg) and intermediate dose (0.8mg), or ○ If there are more than 14 days between the intermediate dose (0.8mg) and first full dose (48mg), or ○ If there are more than 6 weeks between full doses (48mg) ○ After the re-priming cycle, the patient should resume treatment with Day 1 of the next planned treatment cycle (subsequent to the cycle during which the dose was delayed). • **Driving and machinery:** patients should be aware treatment may affect their ability to drive or operate machinery due to the possibility of neurological effects/CRS. • Patients should carry the epcoritamab patient alert card at all times.
References	SPC accessed online 02.02.2024 Blueteq form accessed online 05.02.2024

NB For funding information, refer to CDF and NICE Drugs Funding List

TABLE 1 Cytokine release syndrome grading and management guidance		
Grade	**Recommended Therapy**	**Dose modification**
Grade 1 Fever >/=38° without hypotension or hypoxia	Provide supportive care such as antipyretics and intravenous hydration. Anti-cytokine therapy: Consider anti cytokine 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. See Table 2. Corticosteroids In case of concurrent ICANS, initiation of corticosteroids is highly recommended. Consider dexamethasone 10-20 mg per day (or equivalent).	Hold epcoritamab until resolution of CRS event
Grade 2[a] Fever >/=38° AND/OR Hypotension not requiring Vasopressors AND/OR Hypoxia requiring low flow (</=6l/minute) nasal cannula or blow by	Provide supportive care such as antipyretics and intravenous hydration Anti-cytokine 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 anti cytokine therapy, initiate/increase dose of corticosteroid therapy and consider alternative anti cytokine therapy. In case of concurrent ICANS choose alternative to tocilizumab. See Table 2. Corticosteroids: In case of concurrent ICANS, initiation of corticosteroids is highly recommended. Consider dexamethasone 10-20 mg per day (or equivalent).	Hold epcoritamab until resolution of CRS event.

TABLE 1 continued Cytokine release syndrome grading and management guidance		
Grade	**Recommended Therapy**	**Dose modification**
Grade 3[a] Fever >/= 38°C AND/OR 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	Provide supportive care such as antipyretics and intravenous hydration Anti-cytokine 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 anti-cytokine therapy, initiate/increase dose of corticosteroid therapy and consider alternative anti-cytokine therapy. In case of concurrent ICANS choose alternative to tocilizumab. See Table 2. Corticosteroids: Dexamethasone (e.g. 10-20 mg IV every 6 hours). If no response, initiate methylprednisolone 1000 mg/day.	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 resolved to Grade 2 within 72 hours, epcoritamab should be discontinued.
Grade 4 Fever >/=38°C AND/OR 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 Anti-cytokine 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 anti-cytokine therapy, initiate/increase dose of corticosteroid therapy and consider alternative anti-cytokine therapy. In case of concurrent ICANS choose alternative to tocilizumab See Table 2. Corticosteroids Dexamethasone (e.g.10-20 mg IV every 6 hours). If no response, initiate methylprednisolone 1000 mg/day.	Permanently discontinue epcoritamab
1 CRS graded according to ASTCT (American Society for Transplant and Cellular Therapy) consensus criteria (Lee et al., 2019) a If Grade 2 or 3 CRS occurs with the second full dose or beyond, administer CRS prophylaxis with each subsequent dose until epcoritamab dose is given without subsequent CRS (of any grade).		

Table 2 ICANS grading and management guidance		
Grade	**Recommended therapy**	**Dose modification**
Grade 1[b] 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. No concurrent CRS: • Anti-cytokine therapy not recommended For ICANS with concurrent CRS: • Treatment with dexamethasone[d] • Choose immunosuppressant alternatives[e] to tocilizumab, if possible	Hold epcoritamab until resolution of event
Grade 2[b] 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. No concurrent CRS: • Anti-cytokine therapy not recommended For ICANS with concurrent CRS: • Treatment with dexamethasone[d] • Choose immunosuppressant alternatives[e] to tocilizumab, if possible	Hold epcoritamab until resolution of event
Grade 3[b] 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 raised intracranial pressure: focal/local oedema[b] on neuroimaging[c]	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. No concurrent CRS: • Anti-cytokine therapy not recommended For ICANS with concurrent CRS: • Treatment with dexamethasone ◦ If no response, initiate methylprednisolone 1000 mg/day • Choose immunosuppressant alternatives[e] to tocilizumab, if possible	**First episode:** delay epcoritamab until full resolution of event. **Second episode:** permanently discontinue epcoritamab

Table 2 continued ICANS grading and management guidance		
Grade	**Recommended therapy**	**Dose Modification**
Grade 4b 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]: • deep focal motor weakness such as hemiparesis or paraparesis, Or Raised intracranial pressure / cerebral oedemab, 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	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. No concurrent CRS: • Anti-cytokine therapy not recommended For ICANS with concurrent CRS: • Treatment with dexamethasone ◦ If no response, initiate methylprednisolone 1000 mg/day • Choose immunosuppressant alternatives[e] to tocilizumab, if possible	Permanently discontinue epcoritamab

[a] ICANS graded according to ASTCT ICANS Consensus Grading (Lee et al., 2019)
[b] ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizures, motor findings, raised ICP/cerebral edema) 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.
[d] Dexamethasone should be administered at 10 mg intravenously every 12 hours
[e] Riegler L et al. (2019)

Cycle 1 only: 28 day cycle

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Dexamethasone	16mg	PO	stat	**Given at least 30-120minutes prior to the epcoritamab injection.**
	Paracetamol	1g	PO	stat	
	Chlorphenamine	4mg	PO	stat	
	EPCORITAMAB	**0.16mg Priming dose**	SC		Alternate injection site between the right and left thigh or lower abdomen.
8	Dexamethasone	16mg	PO	stat	**Given at least 30-120minutes prior to the epcoritamab injection.**
	Paracetamol	1g	PO	stat	
	Chlorphenamine	4mg	PO	stat	
	EPCORITAMAB	**0.8mg Intermediate dose**	SC		Alternate injection site between the right and left thigh or lower abdomen.
15 & 22	Dexamethasone	16mg	PO	stat	**Given at least 30-120minutes prior to the epcoritamab injection.**
	Paracetamol	1g	PO	stat	
	Chlorphenamine	4mg	PO	stat	
	EPCORITAMAB	**48mg Full dose**	SC		Alternate injection site between the right and left thigh or lower abdomen.

TTO	Drug	Dose	Route	Directions
Day 1	Dexamethasone	16mg	PO	OD for 3 consecutive days following each weekly administration of epcoritamab. Take with or after food.
	Metoclopramide	10mg	PO	Take 10mg up to TDS when required. Do not take for more than 5 days continuously.
	Loperamide	2-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if required.
	Aciclovir	400mg	PO	BD continuously (plus 3 more months after completion of last epcoritamab treatment dose).
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last epcoritamab treatment dose).
	Allopurinol	300mg	PO	OD, starting 24hrs before first cycle and reviewed after 4 weeks. Prescribe continuing supply if required from cycle 2 onwards.
	Consider antifungal prophylaxis			

Cycle 2 and 3 only: repeat every 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1, 8, 15 and 22	Dexamethasone	16mg	PO	stat	**Given at least 30-120minutes prior to the epcoritamab injection.** **Pre-Med dexamethasone can be omitted in patients who did not experience Grade 2 or 3 CRS with previous dose.**
	EPCORITAMAB	**48mg Full dose**	SC		Alternate injection site between the right and left thigh or lower abdomen.
TTO	Drug	Dose	Route	Directions	
Day 1	Dexamethasone	16mg	PO	OD for 3 consecutive days following each weekly administration of epcoritamab. Take with or after food. **Can be omitted if patients have not experienced Grade 2 or 3 CRS with previous epcoritamab dose.**	
	Metoclopramide	10mg	PO	Take 10mg up to TDS when required. Do not take for more than 5 days continuously.	
	Loperamide	2-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if required.	
	Aciclovir	400mg	PO	BD continuously (plus 3 more months after completion of last epcoritamab treatment dose).	
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last epcoritamab treatment dose).	
	Consider antifungal prophylaxis				

Cycle 4-9 repeat every 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1 and 15	Dexamethasone	16mg	PO	stat	**Given at least 30-120minutes prior to the epcoritamab injection.** **Pre-Med dexamethasone can be omitted in patients who did not experience Grade 2 or 3 CRS with previous dose.**
	EPCORITAMAB	**48mg Full dose**	SC		Alternate injection site between the right and left thigh or lower abdomen.

TTO	Drug	Dose	Route	Directions
Day 1	Dexamethasone	16mg	PO	OD for 3 consecutive days following each weekly administration of epcoritamab. Take with or after food. **Can be omitted if patients have not experienced Grade 2 or 3 CRS with previous epcoritamab dose.**
	Metoclopramide	10mg	PO	Take 10mg up to TDS when required. Do not take for more than 5 days continuously.
	Loperamide	2-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if required.
	Aciclovir	400mg	PO	BD continuously (plus 3 more months after completion of last epcoritamab treatment dose).
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last epcoritamab treatment dose).
	Consider antifungal prophylaxis			

Cycle 10 onwards repeat every 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Dexamethasone	16mg	PO	stat	**Given at least 30-120minutes prior to the epcoritamab infusion.** **Pre-Med dexamethasone can be omitted in patients who did not experience Grade 2 or 3 CRS with previous dose.**
	EPCORITAMAB	**48mg Full dose**	SC		
TTO	Drug	Dose	Route	Directions	
Day 1	Dexamethasone	16mg	PO	OD for 3 consecutive days following each weekly administration of epcoritamab. Take with or after food. **Can be omitted if patients have not experienced Grade 2 or 3 CRS with previous epcoritamab dose.**	
	Metoclopramide	10mg	PO	Take 10mg up to TDS when required. Do not take for more than 5 days continuously.	
	Loperamide	2-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if required.	
	Aciclovir	400mg	PO	BD continuously (plus 3 more months after completion of last epcoritamab treatment dose).	
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last epcoritamab treatment dose).	
	Consider antifungal prophylaxis				