Axicabtagene ciloleucel (Yescarta®) (CAR-T) DLBCL and PMBCL

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of adult patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL) and primary mediastinal large B cell lymphoma (PMBCL), after two or more lines of systemic therapy.	C83 C85	00717a	ODMS 01/03/2022

* This is for post 2012 indications only.

TREATMENT:

Axicabtagene ciloleucel (Yescarta®) must be administered in an NCCP designated CAR-T centre.

Axicabtagene ciloleucel (Yescarta®) is intended for autologous use only.

Facilities to treat anaphylaxis MUST be present when lymphodepleting therapy and CAR-T cells are administered.

Pre-treatment conditioning:

- Lymphodepleting chemotherapy is recommended to be administered before Axicabtagene ciloleucel (Yescarta®) infusion.
- Please refer to the relevant lymphodepletion regimen as decided by the treating clinician at the designated CAR-T centre.

Axicabtagene ciloleucel Administration:

- Please refer to the local CAR-T policy for axicabtagene ciloleucel (Yescarta®) administration information.
- If there is a delay of more than 2 weeks between completing lymphodepleting chemotherapy and the axicabtagene ciloleucel (Yescarta®) infusion the patient may have to be re-treated with lymphodepleting chemotherapy prior to receiving axicabtagene ciloleucel (Yescarta®).
- Tocilizumab for use in the event of cytokine release syndrome and emergency equipment must be available for each patient prior to infusion. The treatment centre must have access to additional doses of tocilizumab within 8 hours.
- The total dose is contained in 1 infusion bag.

Table 1: Axicabtagene ciloleucel Administration

Day	Treatment	Dose	Route
Infuse 2 to 14 days **after** completion of the lymphodepleting chemotherapy	**Axicabtagene ciloleucel (Yescarta®)**	2 x 10^6 CAR-positive viable T cells / kg body weight (maximum of 2 x 10^8 for patients ≥ 100kg)	IV infusion[1]
[1]Through latex-free intravenous tubing without a leukocyte depleting filter, at approximately 10 to 20 mL per minute by gravity flow. All contents of the infusion bag should be infused. NaCl 0.9% solution for injection should be used to prime the tubing prior to infusion and to rinse it after infusion. When the full volume of axicabtagene ciloleucel has been infused, the infusion bag should be rinsed with 10-30mL NaCl 0.9% solution for injection by back priming to ensure as many cells as possible are infused into the patient.			
The product should be administered immediately after thawing. After thawing, the product should be kept at room temperature (20°C-25°C) and infused within 30 minutes to maintain maximum product viability, including any interruption during the infusion.			

ELIGIBILITY:

- Indications as above
- Medical assessment as per local CAR-T assessment form

EXCLUSIONS:

- Known or suspected hypersensitivity to axicabtagene ciloleucel or the excipients
- Known or suspected hypersensitivity to fludarabine or cycloPHOSphamide or the excipients
- Contraindications of the lymphodepleting chemotherapy must be considered
- Active, severe infections (e.g. tuberculosis, sepsis and opportunistic infections)
- Pregnancy or lactation

CAUTION IN USE:

- Due to the risks associated with axicabtagene ciloleucel treatment, infusion should be delayed if a patient has any of the following conditions:
    - Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions or hypotension) from preceding chemotherapies
    - Active uncontrolled infection
    - Active graft-versus-host disease (GVHD)
    - Significant clinical worsening of lymphoma following lymphodepleting chemotherapy.
    - No steroids should be administered without approval of the treating Haematology Consultant

PRESCRIPTIVE AUTHORITY:

- Haematology Consultant working in the area of haematological malignancies who is trained in the administration and management of patients treated with axicabtagene ciloleucel within a designated CAR-T treatment centre.

TESTS:

- Baseline and regular tests carried out in accordance with the hospital's CAR-T Workup Protocol.

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.
- No steroids should be administered without approval of the treating Haematology Consultant.

DOSE MODIFICATIONS:

- No dose modifications are recommended for axicabtagene ciloleucel
- Any dose modification consideration should be discussed with a Haematology Consultant.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Please refer to appropriate NCCP / local Lymphodepletion regimen for further information on anti-emetic regimen.

PREMEDICATIONS:

Please refer to hospital's CAR-T policy

- To minimise potential acute infusion reactions, it is recommended that patients be pre-medicated with paracetamol 1g PO once only 60 minutes prior to axicabtagene ciloleucel infusion and chlorphenamine 10mg IV Injection once only 60 minutes prior to axicabtagene ciloleucel infusion
- No steroids should be administered without approval of the treating Haematology Consultant.

OTHER SUPPORTIVE CARE:

- All patients should receive irradiated blood products (**Refer to local policy).**

Table 2: Suggested Supportive Care[a]

HSV prophylaxis	All patients should receive the following until CD4 count >200/microlitre: • Valaciclovir 500mg once daily PO or • Aciclovir 250mg TDS IV (if oral route not available or ANC < $0.5X10^9$/L) Patients with an active herpes infection should receive the following: • Valaciclovir 1g TDS PO or • Aciclovir 10mg/kg TDS IV (if oral route not available)
Antifungal prophylaxis	Anti-fungal prophylaxis is commenced on the first day of lymphodepleting chemotherapy and continued until neutrophil count ≥$1x10^9$/L and complete remission. • Posaconazole PO 300mg twice daily on first day, then 300mg once daily thereafter.
PJP prophylaxis	**All patients should receive the following for three months post-CAR-T infusion or until CD4 count >200/microlitre:** **PJP prophylaxis is started on the first day of lymphodepleting chemotherapy regimen.** **1st line therapy** • Co-trimoxazole 960mg BD Mon/Wed/Fri PO **2nd line therapy (if allergic to co-trimoxazole or contraindicated):** • Pentamidine 300mg nebule and salbutamol 2.5mg nebule pre-pentamidine, every 4 weeks
Mouthcare	Mucositis WHO grade < 2: • Sodium chloride 0.9% 10ml QDS mouthwash • Nystatin 1ml QDS PO (use 15 minutes after sodium chloride 0.9% mouthwash) Mucositis WHO grade ≥ 2: • Chlorhexidine digluconate 0.12% (Kin®) 10mls QDS PO • Nystatin 1ml QDS PO (use 15 minutes after Kin® mouthwash)
Gastro protection	• Lansoprazole 30mg / omeprazole 40mg once daily PO Or • Esomeprazole 40mg once daily IV (if oral route not available)

Prevention of vaginal bleeding	If required for menstruating female patients until platelets > 50 x10^9/L • Norethisterone 5mg TDS PO if >55Kg • Norethisterone 5mg BD PO if <55kg
Tumour Lysis syndrome	Consider allopurinol in active disease pre CAR-T infusion • Allopurinol 300mg once daily PO for 5-7 days and review
Hepatitis B prophylaxis/treatment	A virology screen is completed as part of CAR-T workup. Hepatitis B prophylaxis or treatment may be initiated in consultation with a Virology Consultant or Hepatology Consultant if required. Options may include: • Lamivudine 100mg once daily PO Or • Entecavir 750microgram once daily PO
Prevention of constipation	Consider laxatives if appropriate e.g. • Senna two tablets (15mg) nocte PO while on ondansetron
Antibiotic standing order	Antibiotic standing order should be prescribed for neutropenic sepsis/neutropenic fever based on previous microbiology and renal function. • Piptazobactam 4.5g QDS IV Plus • Amikacin* 15mg/kg once daily IV *Ciprofloxacin 400mg BD IV may be considered instead of amikacin in cases of renal impairment. Refer to Antimicrobial Guidelines in the SJH Medicines Guide for antibiotic choice where a patient is allergic to any of the above.
Magnesium and potassium standing order	Magnesium and potassium standing orders should be prescribed for all CAR-T patients in accordance with stem cell unit practice as indicated on EPMAR.
VTE prophylaxis	Consider VTE prophylaxis in accordance with SJH policy
Bone Health	Consider calcium and vitamin D supplementation prior to discharge for patients who are on high dose steroids. Other medications for maintenance of bone health may need to be considered as appropriate. • Calcium carbonate and colecalciferol (Caltrate® 600mg/400units) 1 tablet BD

[a]Based on local practice in St James Hospital when V1 of regimen developed

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Axicabtagene ciloleucel is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

- Please refer to the relevant Summary of Product Characteristics and local Stem Cell Transplant Programme PPGs for full details.

DRUG INTERACTIONS:

- The relevant Summary of Product Characteristics and current drug interaction databases should be consulted.

COMPANY SUPPORT RESOURCES/Useful Links:

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

- https://www.yescartahcp.com/large-b-cell-lymphoma

REFERENCES:

1. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol*. 2019;20(1):31-42.
2. Neelapu SS, Jacobson CA, Oluwole OO, et al. Outcomes of older patients in ZUMA-1, a pivotal study of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood. 2020;135(23):2106-2109.
3. Axicabtagene ciloleucel (Yescarta®) Summary of product characteristics EMA. Last updated: 12/01/2024. Accessed Jan 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/yescarta-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	06/05/2022		Dr Larry Bacon
2	04/03/2024	Reviewed.	Dr Larry Bacon

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.