Fludarabine & cycloPHOSphamide Lymphodepletion for Axicabtagene ciloleucel (Yescarta®)

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Lymphodepletion chemotherapy regimen pre-treatment for CAR-T therapy with axicabtagene ciloleucel (Yescarta®) in 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	00608a	N/A

* This is for post 2012 indications only.

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

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

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

Pre-treatment conditioning:

- Lymphodepleting chemotherapy is recommended to be administered before axicabtagene ciloleucel infusion

Axicabtagene ciloleucel Administration:

- Please refer to the local CAR-T policy for axicabtagene ciloleucel (Yescarta®) information

Day	Drug	Dose	Route	Diluent & Rate	Cycle
-5,-4,-3	**Fludarabine**[1]	30mg/m^2	IV	100mL NaCl 0.9% over 30 minutes	1
-5,-4,-3	**Mesna**	200mg/m^2	IV	Slow IV push Into side arm fast flowing NaCl 0.9% infusion	1
-5,-4,-3	**cycloPHOSphamide**	500mg/m^2	IV	500mL NaCl 0.9% over 60 minutes	1
-5,-4,-3	**Mesna**	100mg/m^2	IV	Slow IV push Into side arm fast flowing NaCl 0.9% infusion At 2 and 6 hours after the start of each cycloPHOSphamide infusion	1
0	**Axicabtagene ciloleucel (Yescarta®)**		IV	Please refer to the hospital's CAR-T policy for Axicabtagene ciloleucel (Yescarta®)	

[1]All patients who have received fludarabine should receive irradiated blood products (lifetime recommendation).

Dose rounding:
Fludarabine doses ≤50mg to the nearest 2.5mg and doses ≥50mg to the nearest 5mg,
cycloPHOSphamide to the nearest 20mg.
Mesna to the nearest 100mg

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

Notes:

- The availability of axicabtagene ciloleucel must be confirmed prior to starting the lymphodepleting regimen. If there is a delay of more than 2 weeks between completing lymphodepleting chemotherapy and the infusion, then the patient may require re-treatment with lymphodepleting chemotherapy prior to receiving axicabtagene ciloleucel
- No steroids should be administered without approval of the treating Haematology Consultant

ELIGIBILITY:

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

EXCLUSIONS:

- Hypersensitivity to fludarabine, cycloPHOSphamide, axicabtagene ciloleucel or any of the excipients
- Active, severe infections (e.g. tuberculosis, sepsis and opportunistic infections)
- Pregnancy and lactation
- Haemolytic anaemia

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 local 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:

- Any dose modifications should be discussed with the treating Haematology Consultant
- **Chemotherapy dosing in obese adult patients**: See local policy

Renal and Hepatic Impairment:

- Discuss with the treating consultant if hepatic impairment or if creatinine clearance is < 70mL/min for advice on fludarabine dosing
- Consult the following resources to inform any renal or hepatic dose modification discussions:
    - Summary of product characteristics (SPC) available at http://www.hpra.ie
    - Giraud EL, de Lijster B, Krens SD, Desar IME, Boerrigter E, van Erp NP. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Lancet Oncol 2023; 24: e229
    - Local hospital policy

MANAGEMENT OF ADVERSE EVENTS:

- Refer to local policy

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

Fludarabine: Minimal **(Refer to local policy)**
cycloPHOSphamide: Moderate **(Refer to local policy)**

For information:

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

- 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

Table 1: Suggested Regimen Specific Anti-emetics[a]

Prevention of acute emesis			Prevention of delayed emesis			Comments
Drug	**Dose**	**Admin day**	**Drug**	**Dose**	**Admin day**	dexAMETHasone not used as part of anti-emetic regimen prior to tisagenlecleucel infusion
Cyclizine	50mg PO TDS	-5 to -3	Cyclizine	50mg PO TDS PRN	-2 to -1	
Ondansetron	8mg PO/IV TDS PRN	-5 to -1				

[a]Based on local practice in St James Hospital

OTHER SUPPORTIVE CARE:

Table 2: Other Suggested Supportive Medication[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 (D-5) and continued until neutrophil count ≥1x10^9/L and complete remission. • Posaconazole PO 300mg twice daily on D-5, then 300mg once daily thereafter.
PJP prophylaxis	**<u>All patients should receive the following for three months post CAR-T infusion or until CD4 count >200/microlitre:</u>** **<u>PJP prophylaxis is started on the first day of lymphodepleting chemotherapy (D-5)</u>** **<u>1st line therapy</u>** • Co-trimoxazole 960mg BD Mon/Wed/Fri PO **<u>2nd line therapy (if allergic to co-trimoxazole or contraindicated):</u>** • 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 local hospital antimicrobial guidelines 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 transplant patients in accordance with stem cell unit practice.
VTE prophylaxis	Consider VTE prophylaxis in accordance with local 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) one tablet BD

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

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

HCP Information: http://www.yescartahcp.com/

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. Lee et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. BBMT 2018 12.758
4. Giraud EL, de Lijster B, Krens SD, Desar IME, Boerrigter E, van Erp NP. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Lancet Oncol 2023; 24: e229.
5. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
6. NCCP BACKGROUND DOCUMENT EXTRAVASATION CLASSIFICATION OF SYSTEMIC ANTI-CANCER THERAPY V2 2019. Available at https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/sactguidance/classification.pdf
7. 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
8. Fludarabine Summary of Product Characteristics HPRA. Last updated: 02/06/2023. Accessed Jan 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-035-001_02062023143321.pdf
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Version	Date	Amendment	Approved By
1	06/05/2022		Dr Larry Bacon
2	04/03/2024	Reviewed.	Dr Larry Bacon
2a	19/07/2024	Typographical errors removed	NCCP
3	05/12/2024	Updated suggested regimen specific anti-emetics.	Dr Larry Bacon , Dr Robert Henderson

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.