A.8	CD-19-directed CAR-T cell therapy – relapsed/refractory large B-cell lymphoma – EML
Draft recommendation	☒ Recommended ☐ Not recommended Justification: Based on the body of evidence for the three therapies included in the report I would recommend with conditions -- e.g., price reductions and assurance of tackling barriers for implementation. The decision will have different effects in different countries. For instance, in low-middle income countries it will be more challenging to implement than in higher income countries. The estimated effects show that all three therapies may provide benefits of overall survival, survival without progression, and health-related quality of life, with little to no difference to standard of care in terms of adverse events. Individualized assessments by countries or settings need to be considered to calibrate the cost-effectiveness of these therapies and evaluate the unmet needs to reach an adequate implementation of the interventions such as hospitalization, resources, facilities, and clinical teams with experience in the administration of CAR T-cell therapies.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Relapsed or refractory large B-cell lymphoma (LBCL) is relatively common malignancy with a poor prognosis and aggressive behaviour. The median overall survival of patients with LBCL is of less than 6 to 12 months. High-dose chemotherapy (HDCT) supported by autologous stem-cell transplantation (ASCT) are mainstay therapies with potential for cure. However, not all patients are eligible for this treatment, and of those who are, less than half respond and only about a quarter of patients achieve long-term remission. There is a treatment need among patients who relapse or are refractory to initial treatments, especially after two or more lines of therapies.
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☐ Yes ☒ No ☐ Not applicable Comments: Evidence of low certainty from 3 RCTs (due to inconsistency and indirectness) suggests that cellular immunotherapy with CAR T-cells may improve overall survival compared to the established treatment standard of immunochemotherapy, HDCT and ASCT. The same level of certainty applies for outcomes of overall response, event free survival, and health-related quality of life. Moderate certainty evidence suggest that CAR T-cell therapies likely improves progression free survival.

Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: Moderate certainty evidence suggests that CAR T-cell therapies may result in little to no difference in the occurrence of serious adverse events.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: CAR T-cell therapies are associated with adverse events such as cytokine release syndrome (CRS), reported in all trials in a range of 50% to 90% of patients (1% to 6% as a grade 3), when compared to between 50% to 75% in control groups. Neurologic events are also common, such as the immune effector cell associated neurotoxicity syndrome (ICANS). This syndrome was present in a range of 10% to 60% of patients receiving CAR T-cell therapies as compared to 15% to 17% in the control groups (≥ grade 3 ranged between 2% to 21% in the intervention groups and 3% to 4% in the control groups).
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: Administration of CAR T-cell therapies require special facilities with experienced personnel and clinicians.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: Treatment with Axicabtagene ciloleucel (axi-cel), Tisagenlecleucel (tisa-cel), and Lisocabtagene maraleucel (liso-cel) consists of a single use per patient. All 3 therapies remain expensive, with ICERs reported between 50,000 and >100,000 USD per QALY gained for axi-cel; 78,000 to 103,000 for tisa-cel; and 8,900 for liso-cel, but with substantial variability for all three therapies, depending on the payer perspective and time horizon considered. All three therapies also will require hospitalization and therapies for common adverse events that would need to be considered. Individualized assessments by countries or settings will need to be considered to calibrate the cost-effectiveness of these therapies.

Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☐ No ☒ Not applicable Comments:
Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments: No guidelines related to this topic were found in the WHO guidelines repository