R.1	CAR-T Cell Therapy – Diffuse Large B cell Lymphoma
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Before the introduction of chimeric antigen receptor (CAR)-T cell therapy, patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) ineligible for autologous stem cell transplant (ASCT) had no curative treatment options. Anti-CD19 (or anti-CD20, or anti-CD22) CAR-T cell therapy is proposed as a treatment for patients in this setting, delivering responses and potentially long term responses (or cures) in a minority.
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	CAR-T cell therapy in the form of axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) is proposed as an alternative to palliative chemotherapy in patients with relapsed or refractory (R/R) DLBCL. As currently approved in high resource countries, CAR-T cell therapy is used as third-line treatment for R/R DLBCL.
Have all important studies and all relevant evidence been included in the application?	☒ Yes ☐ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included: All key current data are included, but the field is moving quickly, with multiple randomized studies ongoing and expected to report in 2022 - 2025, and multiple additional CAR-T therapies beyond the two approved types being evaluated.
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☐ Yes ☒ No ☐ Not applicable Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). The preliminary results of a systematic review are provided, and this includes only uncontrolled trial data presented in narrative form (ie no meta-analysis). The quality of evidence is low, given serious risks of bias relating to multiple study design features. The efficacy and safety data all have very low certainty of evidence (GRADE). The data do indicate clinically important complete response rates (40 - 60%), progression-free survival rates of approximately 50% at 6 months, and overall survival rates of 43 - 52% at 18 months. The data for all studies are insufficiently mature to be confident that there are plateaux in the survival curves that reflect the existence of a probable cure fraction.

	Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? No data for children with DLBCL, but CAR-T data are available for children with acute lymphoblastic leukemia and these indicate curative potential for that disease.
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Most toxicity is similar to that observed with ASCT. However CAR-T cell therapy has the additional toxicities of cytokine release syndrome and neurotoxicity due to inflammation. Both may require use of expensive biological anti-inflammatory agents.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☐ No ☐ Not applicable Comments:
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Consistent with the conclusions of the application, with the currently available data, the overall benefit to risk ratio is uncertain. "*The prognosis of people with heavily pretreated relapsed or refractory DLBCL who are not candidates for autologous stem-cell transplantation, or people who relapse after autologous stem-cell transplantation, is generally very poor. In a limited number of study participants CAR-T cell therapy was associated with a median overall survival well above 12 months, reaching 24 months in about half of the cases. Confidence in the data is low due to the lack of a control group and limited internal and external validity. Given the association of CAR-T cell therapy with substantial toxicities which might lead to prolonged hospitalisation or death, and the limited feasibility of CAR-T cell therapy outside authorised centres of excellence, the value of this therapeutic approach is still uncertain*." P 38 of the review
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	As above - the quality of evidence, especially comparative evidence is very low. Nevertheless, the uncontrolled data suggest that a major increment may be achieved with this approach. This clearly remains to be proved.

Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: This is very highly specialized medicine. The treatment is of high intensity and requires dedicated resources, above and beyond the minimum necessary for ASCT. As well as the requirement for quality-controlled apheresis of the T cells, then manufacturing, two-way shipping, and highly specialized medical facilities for infusion and after care, there are major training requirements for all staff involved.
Are you aware of 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 approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments:
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	The review highlights that: - costs are extremely high for the CAR-T products (eg >$300, 000) - costs of care are also very high, with the costs of the total procedure exceeding $500, 000 - modelled incremental cost-effectiveness ratios per quality-adjusted life year (ICER/QALY) range from $50,000 to >$100,000 with lifetime horizons. These have high uncertainty. - some jurisdictions have outcome-based pricing agreements
Any additional comments	Competition among manufacturers may reduce the very high prices currently being paid.

Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	Recommend against inclusion on EML at this point. While CAR-T treatment may prove life-saving for a minority of patients with R/R DLBCL, its comparative effectiveness with other established treatments (eg ASCT) earlier in treatment algorithms is not yet known. Coupled with its very high price and requirements for very advanced technology and staff training, this immaturity of data means that it is premature to consider CAR-T cell therapy for this indication on the EML. Should CAR-T cell therapy prove superior to ASCT in patients with R/R DLBCL, then its clinical impact will be much more certain. As made clear in the summary statement of the review (p3), "*…there are 28 ongoing trials evaluating CAR-T cell therapy for people with r/r DLBCL, of which three are randomised controlled trials (RCTs) to be primarily completed between 2022 and 2025 (BELINDA; TRANSFORM; ZUMA-7), it is important to continue evaluating how evidence will evolve*". Consequently, "*postponing CAR-T cell therapy's potential addition to the complementary list of the Model List of Essential Medicines to one of the next updates (2023 or 2025), if evidence has become compelling*" is recommended.
References (if required)	