R.1	CAR-T cell therapies – relapsed/refractory 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: CART cell therapy is approved for relapsed and refractory hematologic cancers including diffuse large B-cell lymphoma (DLBCL), ALL, CLL and multiple myeloma. Indications for CAR T-cells is also expanding in solid tumors but data is immature. The application is NOT for current listing in EML BUT provides an evaluation of current available evidence for consideration as baseline and serve as baseline for potential future consideration of emerging evidence of this novel therapy for relapsed/refractory DLBCL.
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-cells are indicated in relapsed /refractory DLBCL. Patients relapsing after 2nd line chemo-immunotherapy have poor prognosis, OS of 4 months. Patients with chemotherapy refractory DLBCL or failing ASCT have poor outcomes. Only 7% achieve CR to conventional therapy with brief OS. CAR T-cells have demonstrated high overall response and CR rates with durable remissions in approximately 40% patients in these difficult to treat patients.NO upper age limit as Lympho-depleting therapies for CAR T-cells less toxic. Patient selection essential: PS, co-morbidities and organ and BM function. CAR-T CELLS IN TRANSPLANT ELIGIBLE: First line: CAR T-cells primary refractory, PET-positive after salvage therapy, early relapsing disease and MYC-rearranged lymphomas. This group has a low chance of cure with ASCT. CAR-T CELLS IN TRANSPLANT INELIGIBLE: Palliative chemotherapy with GEM-OX produces CR in 44% but only 13% remain progression free at 1 year. BR remission rate is 15% and median PFS < 4 months.
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: 13 phase 1 &2 studies have been included. In each trial patients varies from 15-269. There are currently no randomised trials.

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). Long term follow-up which is available for a few studies at present shows encouraging improvement in PFS and OS (50-60%) with CAR T-cells. Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? No treatments or trials conducted in low resource settings. In children if studies hold out CAR T-cells may be used either prior to transplant or relapse after transplant. No cut off for age provided the patient has good PS< good organ functions and no medical co-morbidities
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☐ Yes ☒ No ☐ Not applicable Comments: 13 Phase 1 & 2 studies with a heterogenous population including other NHLs. No phase 3 trials conducted. Unclear how many patients were planned, screened and ultimately given CAR T-cells. Dose and number of infusions variable in these studies. Time to response or efficacy (6-24 months) Side effects other than neurotoxicity and CRS not reported. Evidence synthesis: very low certainty of evidence for all outcomes/endpoints. Serious risk of bias across all points. Studies with longer duration of follow up report 5-year PFS and OS in order of 50-70%. If however all studies show significantly more long term improvement in PFS and OS compared to current standard of care maybe phase 3 trials will be considered moot in this poor risk population.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: YES. Special management teams are required to manage these side effects. Identify patients at risk and prevent and manage side effects. 1. Cytokine release storm 2. Neurotoxicities 3. Other toxicities are still being identified.

Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Favourable. However long-term results on survival outcomes are not available compare to standard therapy.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Moderate. No phase 3 randomized trial have been conducted. Patients number enrolled in phase 1 and 2 trials low. Studies highly variable with heterogenous population. Toxicities other then neurotoxicities and CRS not well identified.
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: CAR T-cells require infrastructure and workflow different from those in a general oncology practice. Cell products have to be temperature controlled at all times: preparation, shipping and administration. Programs must have access to apheresis of mononuclear cell collection and storage. Important is chain of custody and identification of the product from collection to shipping to manufacturing facility and back to clinical site and infusion. For toxicities require special inpatient and outpatient teams. Safe administration requires appropriate education, competencies, standard operating procedures and administrative oversight.
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 cost of CAR T-cell therapy is extremely high running into millions of dollars and will be unaffordable or strain health care budgets of LMICs. We have to determine efficacy and cost effectiveness of CAR-T cells as long-term survival data is still not available.
Any additional comments	

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.	At present this application is NOT for approval. CAR T-cells are an area of significant interest and therapeutic relevance and very promising in cancer treatment. Evidence base for these therapies should continue to be monitored on ongoing basis. The currently available data are promising but have significant limitations at this time: small trial sizes (only 3 trials have >100 patients), heterogenous inclusion criteria, outcome data immature and modest certainty of evidence. CAR T cells require a comprehensive health system approach which extends well beyond any future inclusion in EML as these therapies are not medicines per se. However, unless skilled personnel, established processes and procedures with appropriate infrastructure are developed the therapy cannot be delivered across the board. If CAR T-cells are to be used widely the price of the product will need to be lowered significantly to compare more closely with existing therapies There is a strong need and opportunity for WHO to have a leadership and advocacy role to facilitate affordable and equitable access to these important treatment interventions.
References (if required)	