| A.8 | CD-19-directed CAR-T cell therapy – relapsed/refractory large B-cell lymphoma – EML |
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| **Draft recommendation** | ☐ Recommended<br>☒ Not recommended<br>Justification:<br>I do not support the inclusion of CAR-T cell therapy as a therapeutic class or as individual medicines on the EML for relapsed/refractory large B-cell lymphoma.<br>Without indications of variability across studies, CAR-T cell treatment outperforms standard of care with salvage immunochemotherapy in terms of progression free-survival. Nevertheless, the long-term trial follow-up is restricted for all drugs proposed (axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel), and the survival advantage found is now questionable, with one research out of three possibly linking CAR-T to a negative effect.<br>Moreover, cost-effectiveness studies have shown that these medications are not generally cost-effective in most settings at the present rates due to the extremely high current expenses connected with their administration. My main concern is the viability of delivering these medicines and controlling side effects in low-resource areas.<br>I am strongly convinced that CAR-T cell treatments represent a substantial area of research and therapeutic significance for DLBCL and perhaps other cancer indications (such acute lymphoblastic leukemia). I believed that continued monitoring of the evidence supporting these medicines is necessary, because CAR-T cell treatment is a fast developing sector. There is a good chance that in the near future, more sophisticated products (with more effective and less toxic products) will take the place of those that are already on the market. The possible decrease of the secondary effects would allow a safer administration also in low-resource areas. Regarding the second big barrier, the extremely high cost, T-cell production methods outside of industry-scalded centralised manufacturing by companies are now being investigated. Widespread patient access to CAR T cell treatment may be made possible by decentralized manufacturing in hospitals and university medical centers closer to the patients with less expensive products. |

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| Does the proposed medicine address a relevant public health need? | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments:<br>Non-Hodgkin lymphomas (NHLs), which accounted for 4.3% of all cancer cases in the United States in 2015, are the seventh most prevalent kind of cancer worldwide and the most prevalent haematologic malignancy. Diffuse large B-cell lymphomas (DLBCL) account for 40% of all NHLs and 80% of all aggressive lymphomas, making them the most prevalent kind of malignant lymphomas globally.<br>The majority of patients had positive results with first-line immunochemotherapy that combines R-CHOP (Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone). About 30 to 40% of individuals relapse or are resistant to first-line therapy. The time to relapse is the most important factor affecting the salvage rate of immunochemotherapy in second-line therapy, whether in regular or enhanced dosages. Overall, over 60% of patients relapse even with second-line therapies, which consist of salvage immunochemotherapy followed by ASCT. PFS is around 25% at two years in patients with primary progressive illness or recurrence within one year of first-line treatment. As a result, the prognosis for relapsed or resistant LBCLs continues to be dismal. |
| Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication?<br><br>(this may be evidence included in the application, and/or additional evidence identified during the review process) | ☐ Yes<br>☒ No<br>☐ Not applicable<br>Comments:<br>Low to moderate Evidence from three multicentric randomized clinical trials evaluating CAR T-cell therapy in the setting of early relapsing or primary refractory LBCL shows that's CAR T-cell therapy likely improves PFS and EFS when compared to the standard of care including ASCT in 2 over the 3 clinical trials. However, for all medicines proposed (axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel), the long-term trial follow-up is limited, and the survival benefit observed is currently uncertain, with one study out of three potentially associated with a detrimental effect of CAR-T. |
| Does adequate evidence exist for the safety/harms associated with the proposed medicine?<br><br>(this may be evidence included in the application, and/or additional evidence identified during the review process) | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments:<br>CAR T-cell therapy might be associated with substantial toxicity (e.g. CRS or ICANS) there may be little to no difference in the occurrence of serious adverse events when compared to standard of care treatment. |

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| Are there any adverse effects of concern, or that may require special monitoring? | ☐ Yes<br>☒ No<br>☐ Not applicable<br>Comments: |
| Are there any special requirements for the safe, effective and appropriate use of the medicines?<br><br>(e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc) | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments:<br>All three substances, axi-cel, tisa-cel and liso-cel must only be administered in a qualified treatment centre by trained healthcare professionals. These professionals need experience in the treatment of hematological malignancies and must be trained for administration and management of patients treated with each substance.<br>Furthermore, it is also necessary to have an intensive care unit and a team prepared for the management of specific secondary effects such as CRS and ICANS. |
| Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings? | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments:<br>Cost-effectiveness studies have shown that these medications are not generally cost-effective in most settings at the present rates due to the extremely high current expenses connected with their administration. Moreover, currently the infusion of these products and the management of the secondary effects have significant costs associated in addition to that of the drug itself. |
| Are there any issues regarding the registration of the medicine by national regulatory authorities?<br><br>(e.g. accelerated approval, lack of regulatory approval, off-label indication) | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments:<br>The three product have been approved by several regulatory agencies worldwide, but approval in countries with any experience in this field could delay and complicate approval. |
| Is the proposed medicine recommended for use in a current WHO guideline?<br><br>(refer to: https://www.who.int/publications/who-guidelines) | ☐ Yes<br>☒ No<br>☐ Not applicable<br>Comments: |