I.1	Cancer medicines for children – anaplastic large cell lymphoma – EMLc
Draft recommendation	☒ Recommended ☐ Not recommended Justification: I noted that incidence of ALCL ranges from 1.2 per million in children under 15 years, to approximately 2 per million in young adults between 25 and 34 years; European Society for Paediatric Oncology (SIOP Europe) project to summarize anticancer medicines essential to treat children and adolescents with cancer in Europe. Despite the limitation in the evidence presented in the application, treatment protocols including cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide, ifosfamide, methotrexate, prednilosone and vinblastine in ALCL are recognized as the standard of care and are associated with some benefits. Although there is a lack of clinical data available in the paediatric environment, it believed it was unlikely to attain the standard level of evidence needed for EML listings. Based on extrapolation of the well-known benefits and dangers from usage of these medications in adults, for other purposes in children, and as part of conventional cancer care in children, effectiveness and safety in this circumstance might be accepted. Therefore, I recommend the extension of current listings on the complementary list of the EML and EMLc for cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide, ifosfamide, methotrexate, prednilosone and vinblastine to include the indication ALCL. For the suggested indications, each of these medications is utilized in common, multi-modal chemotherapy procedures. The WHO Global Paediatric Cancer Initiative's objectives would be furthered and the best possible cancer treatment for children would be achieved by extending the EMLc indications for these medications. Regarding the ALK inhibitor, I do not support the inclusion of Crizotinib as individual medicines on the EML at this time. I agree that ALK inhibitors for ALCL, and probably other cancer indications (e.g., inflammatory myofibroblastic tumour, Neuroblastoma), are an area of significant interest and therapeutic relevance. I consider that the evidence base for these therapies should continue to be monitored on an ongoing basis, since more potent and less toxic ALK inhibitors are currently being tested in clinical trials and could in the near future replace part of chemotherapy.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Expanding the EMLc indications for these medicines for the treatment of ALCL would support the goals of WHO Global Paediatric Cancer initiative and contribute towards the achievement of the best possible cancer care for children.

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: Although there is a lack of clinical data available in the paediatric environment, it believed it was unlikely to attain the standard level of evidence needed for EML listings. Based on extrapolation of the well-known benefits and dangers from usage of these medications in adults, for other purposes in children, and as part of conventional cancer care in children, effectiveness and safety in this circumstance might be accepted. For Crizotinib: Only two studies published and 1 Abstract with little experience. ALK inhibitors for ALCL, and probably other cancer indications (e.g., inflammatory myofibroblastic tumour, Neuroblastoma), are an area of significant interest and therapeutic relevance. I consider that the evidence base for these therapies should continue to be monitored on an ongoing basis, since more potent and less toxic ALK inhibitors are currently being tested in clinical trials and could in the near future replace part of chemotherapy. Most of the time Crizotinib is used as a bridge to allo Transplant and data on Crizotinib as definitive treatment and on duration of the treatment are lacking.
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:
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: A recent study published by the Children's Oncology group showed addition of Crizotinib to standard treatment resulted in unexpected thromboembolic events in Children.
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: FISH analysis for detection of ALK translocation may be unavailable in LICs.

Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: Regarding Crizotinib, current costs associated with the administration of these medicines are very high with cost-effectiveness analyses finding these treatments not to be cost-effective in most settings at current prices.
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:

Lowe EJ, Reilly AF, Lim MS, Gross TG, Saguilig L, Barkauskas DA, Wu R, Alexander S, Bollard CM. Crizotinib in Combination With Chemotherapy for Pediatric Patients With ALK+ Anaplastic Large-Cell Lymphoma: The Results of Children's Oncology Group Trial ANHL12P1. J Clin Oncol. 2022 Dec 19:JCO2200272. doi: 10.1200/JCO.22.00272. Epub ahead of print. PMID: 36534942.