I.2	Cancer medicines for children – Langerhans cell histiocytosis – EMLc
Draft recommendation	☒ Recommended ☐ Not recommended Justification: LCH affects 4.6 instances per 1 million children under the age of 15 each year. Single-system illness offers an excellent prognosis, with survival rates close to 100%. The result in multi-system illness is variable but still quite high. Patients with multi-system diseases that involved "risk organs" (liver, spleen, and hematological system) and who did not respond to induction treatment after six weeks had a poor prognosis. I support the expansion of the listings on the EMLc for the proposed cancer medicines for Langerhans cell histiocytosis (cytarabine, immunoglobuline i.v., 6-mercaptopurine, methotrexate, prednisone, vinblastine and vincristine). These medicines are all used in standard, multi-modal chemotherapy protocol for the proposed indications. Expanding the EMLc indications for these medicines would support the goals of WHO Global Paediatric Cancer initiative and contribute towards the achievement of the best possible cancer care for children. I am aware that there is a dearth of clinical evidence in the paediatric setting, but I still believed it was unlikely to attain the standard level of evidence needed for EML designations. Based on extrapolation of the well-known benefits and side effects 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. Regarding Cladribine, I do not support the inclusion of Cladribine on the EMLc for treatment of LCH at this time.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: LCH affects 4.6 instances per 1 million children under the age of 15 each year. Single-system illness offers an excellent prognosis, with survival rates close to 100%. The result in multi-system illness is variable but still quite high. Patients with multi-system diseases that involved "risk organs" (liver, spleen, and hematological system) and who did not respond to induction treatment after six weeks had a poor prognosis.

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: Cytarabine, immunoglobuline i.v., 6-mercaptopurine, methotrexate, prednisone, vinblastine, vincristine are all used in standard, multi-modal chemotherapy protocol for the proposed indications. Expanding the EMLc indications for these medicines would support the goals of WHO Global Paediatric Cancer initiative and contribute towards the achievement of the best possible cancer care for children. I am aware that there is a dearth of clinical evidence in the paediatric setting, but I still believed it was unlikely to attain the standard level of evidence needed for EML designations. Based on extrapolation of the well-known benefits and side effects 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. The combination of Cladribine/Ara-C is the current most effective chemotherapy for treatment of refractory LCH with involvement of risk organs. Based on the above studies we can clearly state that Cladribine is an active medicine for treatment of refractory high-risk LCH in children.
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: Based on extrapolation of the well-known benefits and side effects from usage of cytarabine, immunoglobuline i.v., 6-mercaptopurine, methotrexate, prednisone, vinblastine and vincristine 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. Cladribine hematological toxicities are very important, with profound pancytopenia; others toxicities are: infections, septicemia, enteritis, myalgia, tubulopathy and neuropathic pain. Cladribine would be used only in tertiary care centers, with the infrastructure and availability of support therapy (transfusions, antibiotics, antifungal treatment, … This would probably reduce health equity.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments:

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: Yes for Cladribine. Cladribine hematological toxicities are very important, with profound pancytopenia; others toxicities are: infections, septicemia, enteritis, myalgia, tubulopathy and neuropathic pain. These toxicities require careful management with a trained team. Cladribine should be administered only in tertiary care centres, with the infrastructure and availability of support therapy (transfusions, antibiotics, antifungal treatment, … This would probably reduce health equity.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: Yes for Cladribine. Cladribine is averagely expensive, but the main concern is that the supportive treatment is also very expensive and only possible in experimented tertiary centres.
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: