A.5 Blinatumomab – EMLc

Reviewer summary	☒ Supportive of the proposal ☐ Not supportive of the proposal Justification (based on considerations of the dimensions described below): I support the inclusion of blinatumomab on the complementary list of the EMLc for the treatment of pediatric patients with CD19-positive frontline, relapsed, or refractory B-lineage acute lymphoblastic leukemia (B-ALL) based on a positive benefit-risk profile. I thought that B-ALL disproportionately affects children in LICs and LMICs. In comparison to high-income countries (HICs), it is the area with the highest burden, the biggest number of years of life lost, and the lowest cure rates. In contrast to several chemotherapy regimens (e.g., vincristine, cyclophosphamide, daunorubicin, cytarabine), which are linked to significant risks of myelosuppression, infection, and secondary malignancies, blinatumomab is superior in achieving clinical cure, extending overall survival, eliminating minimal residual disease (MRD), and reducing adverse events (Grade ≥3). Corticosteroids and neurotoxicity prophylaxis (e.g., progressive dose escalation during the first week of therapy) can effectively manage blinatumomab-specific adverse effects, such as neurological problems and cytokine release syndrome.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**)	☒ Yes ☐ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? The superiority of blinatumomab in attaining CR, extending overall survival (OS), and producing MRD negativity was shown by meta-analyses of clinical trials that compared it to traditional salvage chemotherapy. **Frontline B-ALL patients** The best outcome for people with ALL is to be cured with frontline therapy. Blinatumomab improved EFS and OS by 15% to 30% in patients with MRD-positive bone marrow at the end of induction and in those who achieve an MRD-negative remission and by similar amounts in those with relapsed disease. For instance, persons with MRD-negative ALL who were between the ages of 30 and 70 were randomly assigned to receive chemotherapy with or without blinatumomab. Because the patients who received blinatumomab had better results, the clinical trial ended early. At three years, their overall survival rate was 85%, compared to 68% in the chemotherapy arm (p=0.002). Furthermore, after 36 months, more events happened in the chemotherapy group but not in the blinatumomab-treated group, further increasing the survival gap. Children have shown similar outcomes to those observed in adults. Children with standard-risk B-ALL were randomized to receive two rounds of blinatumomab in addition to conventional treatment as part of the pediatric study COG AALL1731. When interim analysis revealed that blinatumomab produced better results, the study was terminated early. At a median follow-up of 2.5 years, the estimated 3-year disease-free survival (±SE)	☒ Yes ☐ No ☐ Not applicable

was 96.0±1.2% with blinatumomab and chemotherapy and 87.9±2.1% with chemotherapy alone (difference in restricted mean survival time, 72 days; 95% confidence interval, 36 to 108; P<0.001 by stratified log-rank test). The estimated 3-year disease-free survival among patients with an average relapse risk was 97.5±1.3% with blinatumomab and chemotherapy and 90.2±2.3% with chemotherapy alone **Relapsed/Refractory B-ALL patients** Blinatumomab has a number of advantages over traditional chemotherapy for pediatric patients with relapsed or refractory B-ALL. For instance, DFS at 4 years improved from 54% to 73% (p=0.02) and OS at 4 years improved from 85% to 97% (p=0.02) in the Children's Oncology Group randomized trial of children with ALL in first bone marrow relapse (without extramedullary relapse) (Figure 7). Because patients who fail chemotherapy are likely to switch to a blinatumomab-containing regimen, which may result in successful salvage therapy in the next line of treatment, DFS and EFS may be more accurate indicators of blinatumomab efficacy.	
Does adequate evidence exist for the safety/harms associated with the proposed medicine? When compared to traditional chemotherapy, blinatumomab has a better safety record. Principal side effects of Blinatumomab treatment: **Cytokine release syndrome** (CRS): Although CRS is a known concern, it is usually mild to moderate and can be efficiently treated with tocilizumab or corticosteroids, as well as with a brief halt in treatment. **Neurotoxicity**: The most dangerous side effects of blinatumomab are neurologic ones, such as encephalopathy and seizures. However, there is a low likelihood of severe, long-lasting neurologic consequences, and these occurrences are mostly reversible. **Reduced hematologic toxicity:** Unlike chemotherapy, blinatumomab does not cause significant myelosuppression, reducing the risk of life-threatening infections, bleeding, and transfusion dependence. By contrast, the hazards of severe myelosuppression, infection, mucositis, organ damage, and subsequent malignancies are significant with traditional chemotherapy, especially when the treatment is prolonged or escalated. Last but not least, blinatumomab's advantages in randomized clinical studies involving frontline and relapsed/refractory patients show its safety profile in comparison to other treatments.	☒ Yes ☐ No ☐ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?	☒ Yes ☐ No ☐ Not applicable
Are there any special requirements for the safe, effective and appropriate use of the medicines? Because blinatumomab is administered by continuous intravenous infusion via central venous access over a period of 28 days per cycle and usually up to five treatment cycles, I expressed concerns about the viability of applying this medication in LMICs and LICs. I did point out, though, that a subcutaneous formulation is currently being developed and might significantly allay these worries.	☒ Yes ☐ No ☐ Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings? Although blinatumomab is relatively expensive, it has proven cost-effective in both frontline and relapsed settings because it induces durable remissions and reduces the need for more expensive interventions, such as repeated hospitalizations, intensive chemotherapy, HSCT, and CAR-T cell therapy. I recognized that blinatumomab faces financial and accessibility obstacles in LMICs and LICs; nevertheless, considering its potential for cure, multisectoral assistance, including	☒ Yes ☐ No ☐ Not applicable

access initiatives like those that have already made blinatumomab available in certain LMICs, may prove to be cost-effective	
Is the medicine available and accessible across countries? I emphasized the WHO's Global Initiative for Childhood Cancer's ongoing initiatives to enhance the survival of children with cancer worldwide and expand access to life-saving cancer medications.	☐ Yes ☒ No ☐ Not applicable
Does the medicine have wide regulatory approval?	☐ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☒ No ☐ Not applicable