A.5 Blinatumomab – EMLc

Reviewer summary	☒ Supportive of the proposal ☐ Not supportive of the proposal Justification (based on considerations of the dimensions described below): Having considered the application for listing of blinatumomab on EMLc, the advice of the Cancer Experts Committee, the recently submitted supplementary application for extension of the application to include adolescents up to 19 yoa, and the existing peer-reviewed literature, including data published in the last 6 months, my view is that blinatumomab is a major advance in therapy for patients with B-lineage ALL across all age ranges, and that its impact in low-and middle-income countries (LMICs) should substantially increase the number of lives saved through treatment. That benefit is not restricted to children under 13 years of age, nor diminished in adults. High quality data (randomized trials, meta-analyses) indicate that blinatumomab incorporation into multi-agent regimens: - improves disease-free survival in children with standard-risk B-ALL when used in the front-line (Hazard ratios [HR] not reported due to potential non-proportionality) - improves survival in adults with B-ALL when used in the front-line (HR 0.41; 95% CI 0.23 to 0.73) - Improves survival in adults (HR 0.71; 95% CI, 0.55 to 0.93) and children (HR 0.43 (95% CI, 0.18-1.01) after relapse. Single arm trial data also indicate that it is highly effective in infantile B-ALL, with effect size compared to historical controls using best-previous chemotherapy regimen commensurate with those seen in randomized trials in older children and adults for disease-free survival. The toxicities of blinatumomab are reduced when compared to the existing alternative of intensive cytotoxic chemotherapy blocks, particularly with respect hematological toxicites and infections. “New” toxicities of cytokine release syndrome and neurotoxicity are important, but typically reversible, and their impact is small compared to the magnitude of the overall clinical benefits. Consequently, blinatumomab has a very major positive impact on survival, leukemia-free survival, safety and quality of life. Ideally it should be available for treatment of all patients with B-ALL. In the long term, its greatest impact will be when used as part of front-line treatment regimens, where it will increase the cure fraction, and thereby minimise both loss of life and costs and toxicities incurred treating relapsed disease. Until first-line use is the normal, patients, who relapse and have not previously received blinatumomab, will also greatly benefit and a significant proportion of them will be cured. Blinatumomab administration is complex and requires trained staff and specialised pumps that enable prolonged continuous infusion in ambulatory care. Other than cost, this is the major limitation for widespread use in LMICs. However, as the application outlines, training programs are available and implementation has been successful through partnerships. Consequently, this potential barrier should not be rate-limiting ie where curative therapy is being provided for ALL, this therapy should also be administrable. Blinatumomab is considered cost-effective in high income countries in adults and children despite high acquisition costs. Affordability for LMICs will depend on tiered and negotiated pricing. It is welcome to see that AMGEN is committed in principle to making this ground-breaking, highly effective product available for children through partnerships. A key to cost-effectiveness will be ensuring that use follows established protocols. These will likely change over time, as further evidence emerges, so adherence to guidelines and widely accepted regimens should be highly encouraged, if not mandated. Availability for use in children, adolescents and young adults (ie <40 years of age) could be a priority in countries where financial constraints preclude providing the drug for all age groups and where societal values place higher weightings for life-saving therapies for young people over otherwise equivalent health gains for older people.

	Blinatumomab is widely approved, and various programs have made the drug available in selected LMICs. These programs have both proved feasibility and will provide invaluable assistance during any implementation phases.
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? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;)	☒ Yes ☐ No ☐ Not applicable
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;)	☒ 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? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings?	☒ Yes ☐ No ☐ Not applicable
Is the medicine available and accessible across countries? (e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes)	☒ 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