A.32 Zanubrutinib – EML for the treatment of CLL/small lymphocytic lymphoma

Reviewer summary	☐ Supportive of the proposal ☒ Not supportive of the proposal Justification (based on considerations of the dimensions described below): • Data on overall survival were unconvincing (i.e., no significant difference in overall survival HR).

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) This application proposes inclusion of zanubrutinib on the EML for the treatment of chronic lymphocytic leukemia and small lymphocytic leukemia is a re-submission. The treatment for CLL is a rapidly evolving field and new studies evaluating combination regimens with zanubrutinib (e.g., triplet combination of zanubrutinib + venetoclax + obinutuzumab) are ongoing. Data supported better progression free survival gains with zanubrutinib when compared to ibrutinib – which is a TKI on the EML. However, data on overall survival – were unconvincing. Two pivotal randomized trials evaluated overall survival in patients randomized to zanubrutinib. After a median 42.5 months of follow-up, there was no significant difference in overall survival when zanubrutinib was compared to ibrutinib (HR for death 0.77, 95% CI 0.55 to 1.06). Median overall survival was not reached in either group [1]. Similarly, the randomized trial comparing zanubrutinib to a combination of bendamustine and rituximab found no difference in overall survival (HR, 1.07; 95% CI, 0.51-2.22) [2]. Finally, the improved safety profile with zanubrutinib may well be blurred as ibrutinib was used at a relatively high dose, likely leading to an overestimate of the difference in adverse events between zanubrutinib and ibrutinib in the reported results. Side effects:	☒ Yes ☐ No ☐ Not applicable 1) Brown, J.R., et al., Sustained benefit of zanubrutinib vs ibrutinib in patients with R/R CLL/SLL: final comparative analysis of ALPINE. Blood, 2024. 144(26): 2706-2717. 2) Tam, C.S., et al., Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. Lancet Oncol, 2022. 23: 1031-1043

Very common (>10%): Upper respiratory tract infection, pneumonia, urinary tract infection, neutropenia, thrombocytopenia, anemia. Dizziness. Bruising, contusion. Bleeding, hematoma, hematuria. Hypertension, cough, diarrhea, constipation. Skin rash.Muscle pain, joint pain, back pain. Fatigue. Decrease in neutrophil count, decrease in platelet count, decrease in blood hemoglobin. Common (1–10%): Lower respiratory tract infection, bronchitis. Atrial fibrillation, atrial flutter. Petechiae, purpura, ecchymosis. Nosebleed. Itching. Asthenia (general weakness). Peripheral edema. Uncommon (0.1–1%): Reactivation of hepatitis B. Gastrointestinal bleeding.Tumor lysis syndrome.	
Are there any issues regarding price, cost-effectiveness and budget implications in different settings? Very expensive drug	☒ 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? EMA, FDA yes Zanubrutinib has regulatory approval in more than 65 markets globally	☒ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☐ No ☐ Not applicable