A.52	Zanubrutinib – chronic lymphocytic leukaemia/small lymphocytic lymphoma – EML
Draft recommendation	☐ Recommended ☒ Not recommended Justification: I do not support the inclusion of zanubrutinib on the EML for treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma at this time. Progression-free survival is significantly improved in patients treated with zanubrutinib versus bendamustine and rituximab (BR) (HR 0·42) but not overall survival. Of note, deaths are numerically higher in the zanubrutinib arm, and high rate of hemorrhage and secondary primary malignancies (21%) is concerning. The BR control arm is suboptimal and should have been rather than time limited BR. In conclusion, in my opinion, the lack of survival advantage and the safety signal suggest that more data and longer follow up are needed before making a recommendation. It was noted that while data supported progression-free survival gains from zanubrutinib when compared to ibrutinib, another TKI recommended by WHO as an essential medicine, the magnitude of these gains may be limited, and that few long-term and real-world data were available. Furthermore, high rates of toxicity (particularly neutropenia) and limited information on prices with uncertain cost–effectiveness (given lower doses that can be used with ibrutinib as compared to those proposed in the application) are acknowledged as limitations for the procurement and use of zanubrutinib.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Chronic lymphocytic leukaemia is the most common form of leukaemia in western countries. Globally, the number of deaths due to chronic lymphocytic leukaemia has increased in 70% from 1990 to 2017. However, the age-adjusted death rates have decreased in high-income regions while increased in Central Sub-Saharan Africa, East Asia, and Southeast Asia. While being mostly regarded as an indolent disease, it nonetheless has a wide range of clinical manifestations and is a life-limiting condition. All individuals with CLL/SLL who require therapy will eventually relapse since the illness is still incurable. There is a wide range in the prognosis for various CLL/SLL patients, with the median overall survival (OS) being around 10 years. While 20% of patients present with a very aggressive appearance and have a median OS of 1.5–3 years, other people can live for years.

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: The magnitude of these gains may be limited, and there are few long-term and real-world data available, despite evidence showing progression-free survival gains from zanubrutinib when compared to ibrutinib, another TKI recommended by the WHO as an essential medication.
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: High rates of toxicity (particularly neutropenia). More data on toxicity are needed.
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:
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☐ No ☐ Not applicable Comments: Furthermore noted as restriction for the purchase and usage of zanubrutinib is the lack of pricing information and questionable cost-effectiveness (given lower dosages that can be used with ibrutinib than those recommended in the application).

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: