A.39	ZANUBRUTINIB – Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Relapsed CLL and SLL are significant health problems. In recent years, new targeted therapy options for treatment have markedly improved outcomes in randomized trials. BTK inhibitors, such as ibrutinib and zanubrutinib, are one class of drug that has proved transformative. In countries where ibrutinib and other approved BTK inhibitors such as acalubrutinib are available, there is minimal unmet need for an additional BTK inhibitor, such as zanubrutinib. However, in countries where there is no access to BTK inhibitors, there can be high unmet need, especially among patients whose CLL/SLL carries either deletion of chromosome 17p or *TP53* mutations.
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	The proposed role is as an alternative to current EML listed drugs applicable for CLL and SLL ie chlorambucil and rituximab. No randomised trials have been reported as yet for zanubrutinib compared to these drugs. Zanubrutinib is also an alternative to ibrutinib (also being considered for the EML) and a randomised Phase 3 trial has just been reported in preliminary fashion at the June 2021 European Society of Hematology Annual Meeting.
Have all important studies and all relevant evidence been included in the application?	☐ Yes ☒ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included: The great majority of data are included. However, the very recent preliminary data on the randomised trial of zanubrutinib versus ibrutinib which were presented in preliminary abstract form at EHA June 2021 are understandably not included. Without formal peer review through full publication they cannot be considered as key data.

Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☒ Yes ☐ No ☐ Not applicable Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). The data provide strong evidence for activity of zanubrutinib in CLL_SLL, but there is no robust evidence as yet of comparative effectiveness against drugs currently listed on the EML. Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? No
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Zanubrutinib has a safety profile consistent with that of other BTK inhibitors. The claim of superiority over ibrutinib can only be judged when the mature results of the single randomized Phase 3 trial are fully reported.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments:
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	This drug has a favourable benefit:risk ratio.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	The evidence for activity is compelling, but there are no high quality data provided for comparative effectiveness. This limits the panel's ability to consider the drug for inclusion on the EML.
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments:

Are you aware of 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: The drug has very limited approval internationally at this point. Approved in CLL/SLL by National Medical Products Administration in China (June 2020) Approved by FDA for relapsed mantle cell lymphoma Not widely approved for CLL/SLL around the world
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments:
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	The application indicates that monthly treatment cost for zanubrutinib in China is 21,188 RMB, whilst the international standard BTK inhibitor, ibrutinib has a cost of 17,010 RMB per month in China for CLL/SLL patients. Comparatively, the first-generation BTK inhibitor (Ibrutinib) is listed. Zanubrutinib appears more expensive that the class originator (ibrutinib), and at this point in time only has registration in China. Both zanubrutinib and ibrutinib are very high cost drugs given that treatment is typically ongoing for many years. Affordability is therefore a major barrier for uptake of these drugs in low resource health settings.
Any additional comments	Without formally and completely reported data from randomised trials, it is not possible to assess the drug for inclusion on the EML for this disease setting. Nevertheless, the randomised data across the BTK inhibitor class do indicate major advantages for patients with CLL/SLL over existing drugs on the EML. Consequently, if BTK inhibitors are considered appropriate for listing on the EML, then competition within the class may lead to improved value for money. In that regard, the formal results of the randomised trial between zanubrutinib and ibrutinib could prove informative.
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	Zanubrutinib is an effective BTK inhibitor. Given the Phase 2 data available, it may become an appropriate alternative for any other BTK inhibitor listed on the EML for the indication of CLL/SLL. That determination would be best informed by the final results of ongoing trials.
References (if required)	