A.40	Zanubrutinib – mantle cell lymphoma
Does the application adequately address the issue of the public health need for the medicine?	☐ Yes ☒ No ☐ Not applicable Comments:
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.	Mantle cell lymphoma is a rare, aggressive variant of non-Hodgkin lymphoma, primarily affecting older patients. For the proposed medicine, there are only phase I (dose-finding, not MCL specific population) and II (RR MCL n=74) trial data available. They show objective response rates above 80%. There are, however, no direct head-to-head comparisons with other treatments for this disease. So: the only data available is from early phase trials, small patient numbers and short follow-up. Indirect phase II and III comparative data against acalabrutinib and ibrutinib suggest greater response rates for zanubrutinib than comparators.
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: Only phase 1-2 data
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☐ Yes ☒ No ☐ Not applicable Only phase 1-2 data and short follow up data.
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☐ Yes ☒ No ☐ Not applicable Only phase 1-2 data. Zanubrutinib is associated with significant haematological toxicity. Compared to ibrutinib, less atrial fibrillation but same rate of major bleeding and more minor bleeding. Nearly one-quarter of patients experience grade 3 and 4 infections (related to neutropenic toxicity), including fatal infections.

Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: See toxicity profile
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Insufficient data to justify inclusion in the EML list.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Difficult given the limited data available
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: Haematological toxicity
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: Zanubrutinib received expedited approval in China, and orphan drug accelerated approval by the FDA for this indication. FDA approval for patients who have received at least 1 prior therapy.
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.	This is a high priced medicine for a rare indication, only tested in phase 1-2, without long-term data, with major haematological toxicity. The current place is in patients who have at least received one prior line of therapy, so not a medicine for first-line treatment.
Any additional comments	

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.	Advice: do not include in the EML list given current information
References (if required)	