A.40	ZANUBRUTINIB – RELPASED/REFRACTORY MANTEL CELL LYMPHOMA

Does the application adequately address the issue of the public health need for the medicine?	☐ Yes ☒ No ☐ Not applicable Comments: It is a rare disease with an overall indolent but subsequent to serial recurrences an reduced QoL and median OS of 3-4 years.
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.	Relapsed / refractory Mantle cell lymphoma is managed with Bortezomide , lenalidomide , venetoclax . Other drugs Burtons tyrosine kinase inhibitors are ibrutinib, acalbrutinib are supposedly more tolerable in fragile patients It is a 2nd line BTK with better tolerability to IBRUTINIB within the same class.
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:
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). Median follow up of the 2 studies 9-10months, one phase 1 b and another phase2 trial with sample size 43 and 89 respectively . ORR was > 80% in both studies , the phase 1b demonstrates an 18month median PFS and not reached in phadse 2 trial . No phase 3 trials to confirm results from small studies. In one study CR after 18 months was 58.8% , DOR 19.2 months . In comparison to other drug ibrutinib , a CR rate of 20%in a phase 3 trial the gain in PFS of 3.4 month . Phase 3 trial planned but not enough evidence generated to confirm added benefit. No large QoL studies to support tolerance benefits. Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? Studies are quite small for any meaningful recommendations to be made in high risk patients So far , not recommended in children, pregnant and lactating mothers. Studies conducted in china in transitional economy . , there are some comparative results for Asian (75%) versus non Asians (21% whites) no differences , quite narrow in application , no non whites..

	The endpoints are similar to phase 2 trial regimen of Rituximab ,bendamustine , cyclophosphamide and cytarabine ,ORR 80%, CR 60% DOR 18 MONTHS , 2 YR PFS 70%.(Visco, Carlo, et al. "Combination of rituximab, bendamustine, and cytarabine for patients with mantle-cell non-Hodgkin lymphoma ineligible for intensive regimens or autologous transplantation." J Clin Oncol 31.11 (2013): 1442-1449.)
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Liver failure, renal failure, bleeding in 57% of patients, 8% discontinuation less than 11% of comparator, less Atrial fibrillation rates , grade 3 pneumonia 7% drug related deaths
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Use of concomitant anticoagulation therapies to prevent bleeding Patients with cardiac risk factor at greater risk of grade 3 AF Risk of secondary skin cancer with sun exposure , caution in tropics. High risk of grade 3 infections in this group requiring special monitoring
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	The Benefit to risk is favourable in regard to high ORR , DOR of greater than 18 months and CR of . 60% , risk of grade 3 or higher AE is relatively low
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	The quality of evidence is low, small numbers , non randomised phase 1 /2 trials, short follow up , no quality of life assessment.
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: Drug interactions Infection monitoring Cardiac monitoring Liver function monitoring

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: Accelerated approval in China. Accelerated approval by FDA US in November 2019 based on impressive ORRBut continued approval will be dependent on confirmatory trials , adopted Chinese data. Majority of population were Chinese. Wide time lapse between 2 agencies indicating discrepancies It is also FDA approved for waldenstroms macroglobulinemia and CLL.
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 current cost assessment prove this drug to be non cost-effective option for LMIC. Access will be limited to UMIC and HIC countries. It also requires specialized health monitoring in less accessible health systems.
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.	In spite of the high ORR , this drug does not add additional significant benefit over existing options. The results from studies are not confirmed in large RCT and reproduced in results reproduced. There is no quality of life assessment in all trials. In view of the rarity of this disease , ie would be difficult to recommend large RCT , but rather I recommend we await results of the impending phase 3 trial .
References (if required)	Hanel et al. Emerging therapies in mantle cell lymphoma. Journal of Hematology and Oncology 13,79(2020) Visco, Carlo, et al. "Combination of rituximab, bendamustine, and cytarabine for patients with mantle-cell non-Hodgkin lymphoma ineligible for intensive regimens or autologous transplantation." J Clin Oncol 31.11 (2013): 1442-1449.