A.19	Ibrutinib – Chronic Lymphocytic Leukaemia with del 17p
Does the application adequately address the issue of the public health need for the medicine?	☐ Yes ☒ No ☐ Not applicable Comments: A medication likely to impact outcomes for the most common form of leukaemia in the west with rising death rates in LMIC makes a strong case especially for patients with 17p deletion known to be refractory to chemotherapy and other systemic therapies . Of note, P17 deletions makes less than 10% of new cases and up to 50% of relapsed / resistant cases. cases This information was withheld in the document
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.	Ibrutinib is a small molecule drug that binds with Brutons Tyrosine kinase permanently to prevent proliferation of B cells promoting cell death in B cell cancers . Its introduction into managing CLL has reportedly improved outcomes either alone or in combination with existing protocols. Enlisting in the Model list is expected to improve cost effectiveness and access worldwide Chlorambucil , fludarabine , cyclophosphamide , Bendamustine, Rituximab, are listed in Model list of CLL care used in combination Obinutuzumab , ofatumumab are other anti-CD20 not in list but approved by various national agencies for treatment of general CLL
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: Trials specific to CLL with P17 deletion subtypes where not largely included and all submissions where for general CLL. There is no strong data provided here to elucidate the difference in outcomes for those with or without 17p/TP53 deletions in spite of existing publications Del(17p) is known to directly interplay with anti CD 20 and other chemotherapy pharmacokinetics resulting in early treatment resistance . Rituximab in combination with Ibrutinib did not improve PFS but CR rates in p17 del(12 vrs 26 months) (ALLIANCE A041202 PHASE 3 STUDY) Bagacean C al. j.immunotherapy cancer7,22(2019. A study specific for p17 del in 230 patients additionally provides evidence even though estimated to the efficacy of ibrutinib. Jeffrey jones et al ,Br J Haematol 182;504-512.

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). As a single agent , patient derived improved PFS and OS somewhat compared to combination therapies that included anti CD20 medications . HR for OS in metanalysis is 0.44 , for PFS 0.2 with absolute benefit of 50 months with narrow CI in relapsed / refractory states. These results were not specific to delP17 subtypes even though small numbers were included in the studies presented. The results are extrapolated to suggest benefit in del P17 subtypes. In RESONATE 2, Ibrutinib versus chlorambucil PFS HR 0.15 89 VRS 34% AT 2 YRS, 70 VRS 12 % at 5 years, OS HR 0.45 95 VRS 84% AT 2 YRS , 83 VRS 68% AT 5 YRS Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? No , no safety information available in pregnancy and renal impairment but with young adults very tolerable /
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: listed the most common AE NON HEMATOLOGICAL, , Diahorrhea, , Discussed major contraindications and toxicities hepatic impairment, atrial fibrillation – 16%. major bleeding 11%and hypertension26%. Quality of life was not adequately explored as an end point in any of the trials .
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Atrial fibrillation, liver function, hypertension and Diahorrhea must be monitored P17 deletion must be detected.
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Has favourable benefit to all patients with CLL , but requires strong health system The frequency of grade 3 and 4 toxicity was the same as other combination therapies.

Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	The power of the studies were mostly low, evidence was considered strong is some studies and replicated . will rate overall quality as moderate.
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: Anticoagulation to be monitored, Cardiovascular monitoring P17 deletion detection.
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:
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.	There are studies on the cost effectiveness of ibrutinib across Europe, Australia, japan , US . many of these studies have severe limitations. Ibrutinib was similar to other immunotherapy drugs for CLL in cost evaluation and considered not cost-effective. Specialized medical systems are required for diagnosis and monitoring. There is currently limited access in LMIC , even though its use has been recorded in India.
Any additional comments	The current title of the application is misleading and should changed to read Ibrutinib in high risk or relapsed Chronic lymphocytic leukaemia
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.	My recommendation will be to change the title of the application as the evidence provided is skewed towards high risk CLL including del p17. There is moderate evidence it improves PFS in high risk group even as a single agent who otherwise have short PFS and poor survival. Concerns are the high cost and the need for prompt recognition and management of toxicities.

References (if required)	