A.19	Ibrutinib for Chronic Lymphocytic Leukaemia
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Chronic lymphocytic leukaemia is the most common form of leukaemia in western countries. Its incidence is higher in North America and Europe and lower in Latin America and Asia.
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 (Imbruvica), alone or with rituximab (Rituxan) **Bendamustine and rituximab (or another monoclonal antibody)** **High-dose prednisone and rituximab** **FCR: fludarabine, cyclophosphamide, and rituximab** **Chlorambucil and rituximab (or another monoclonal antibody)** [Bold: Currently listed on WHO EML 2019 complementary list]
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). The meta-analysis of these three studies showed that the use of ibrutinib as a first or second line of treatment probably increases the overall survival and the progression free survival (moderate and high certainty evidence respectively). Ibrutinib increases the overall survival (HR 0.44, 95% CI 0.20 - 0.97; moderate certainty evidence) and the progression free survival (HR 0.20, 95% CI 0.15 - 0.27; high certainty evidence). In terms of absolute effect, the use of ibrutinib prolongs progression free survival in at least 50 months (approximately 4 years). There is indication of survival benefit specifically, in the 17p- first-line sub-group. Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? iLLUMINATE is a multicentre, randomised, open-label, phase 3 trial done at 74 academic and community hospitals in Australia, Canada, Israel, New Zealand, Russia, Turkey, the EU, and the USA. HELIOS study was conducted in 21 countries. RESONATE was conducted in 94 centres.

<table>
<tr><td>Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?</td><td>☒ Yes
☐ No
☐ Not applicable
Comments:
<table>
<tr><th rowspan="2">Outcomes</th><th rowspan="2">Relative Effect (CI 95%)</th><th colspan="3">Anticipated absolute effect</th><th rowspan="2">Certainty of the Evidence (GRADE)</th></tr>
<tr><th>WITH Ibrutinib</th><th>WITHOUT Ibrutinib</th><th>Difference (CI 95%)</th></tr>
<tr><td>Hypertension
8 RCTs
(n= 2,580)</td><td>RR 2.82
(1.52-5.22)</td><td>107
per 1000</td><td>38
per 1000</td><td>69 more
(20 to 160 more)</td><td>⨁⨁⨁◯[a]
MODERATE</td></tr>
<tr><td>Atrial fibrillation
8 RCTs
(n= 2,580)</td><td>RR 4.68
(2.36-9.28)</td><td>26
per 1000</td><td>7
per 1000</td><td>19 more
(10 to 58 more)</td><td>⨁⨁⨁⨁
HIGH</td></tr>
<tr><td>Major bleeding
4 RCTs
(n=1,518)</td><td>RR 1.66
(0.96-2.85)</td><td>322
per 1000</td><td>200
per 1000</td><td>122 more
(8 fewer to 370 more)</td><td>⨁⨁⨁◯[b]
MODERATE</td></tr>
</table></td></tr>
<tr><td>Are there any adverse effects of concern, or that may require special monitoring?</td><td>☒ Yes
☐ No
☐ Not applicable
Comments: The use of ibrutinib (in comparison with regimens without ibrutinib) probably results in 60 more cases of hypertension (95% CI from 20 to 160 more, moderate certainty evidence); 19 more cases of atrial fibrillation (95% CI from 10 to 58 more, high certainty evidence); and 122 more bleeding events (95% CI from 8 fewer to 370 more, moderate certainty evidence).</td></tr>
<tr><td>Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)</td><td>Uncertain
The Length of survival is a positive benefit, but the side effects/adverse effects of hypertension, major bleeding and atrial fibrillation are also of concern. Resistance development to ibrutinib is also not presented.</td></tr>
<tr><td>Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)</td><td>High</td></tr>
<tr><td>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)</td><td>☒ Yes
☐ No
☐ Not applicable
Comments: Due to side effects of hypertension, major bleeding and atrial fibrillation, monitoring is required which may necessitate in patient stay or administration at a high resourced and specialized centre.</td></tr>
</table>

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.	Studies have indicated that this medication is not a cost-effective option. Three agencies, The Canadian Agency for Drugs and Technologies in Health (CADTH, https://www.cadth.ca; Canada), The National Institute for Health and Care Excellence (NICE, https://www.nice.org.uk; UK) and The Pharmaceutical Benefits Advisory Committee (PBAC, https://www.pbs.gov.au/pbs/home; Australia), published a report evaluating ibrutinib. All three recommended covering the medication but only in specific subgroups of patients and with costs that are secret to public. A study by Irwin et al (2021) indicated that the per patient per month (PPPM) all-cause total costs were comparable between ibrutinib monotherapy (IbM) patients and bendamustine hydrochloride used in combination with rituximab (BR) patients ($12,767 vs. $12,268; p=.34) during the 12-month follow-up period. IbM patients had significantly higher PPPM all-cause inpatient costs than BR patients ($1,383 vs. $722; p=.03). IbM patients had significantly higher PPPM outpatient pharmacy prescriptions costs ($8,575 vs. $886, p<.001), while BR patients had significantly higher PPPM outpatient medical costs (primarily due to infusion costs) than IbM patients ($10,660 vs. $2,809, p<.001). CLL-related total costs were also comparable between IbM and BR patients ($11,042 vs. $10,407; p=.16). IbM patients had significantly higher CLL-specific inpatient costs than BR patients ($1,257 vs. $466; p=.01). IbM patients had significantly higher PPPM CLL treatment (prescription/medical) costs ($8,358 vs $7,530; p=.004), while IbM patients had significantly lower higher PPPM CLL-related outpatient medical costs ($1,427 vs $3,033; p<.001).
Any additional comments	Could be used in sub-groups only after other more cost-effective therapies fail. Patent expiry is in 2031. Based on pricing information this product will not be within the budgets of most middle and low income countries.

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.	The health system requirements are complex, and require specific including diagnostic capabilities to identify the appropriate cohort of patients, in addition to monitoring for the reported relevant side effects. Thus, the reviewer recommends that addition of this product requires careful debate and that the treatment regimens already listed in the WHO EML Complementary list could be used. The clinical benefits associated with their use [On the WHO EML: bendamustine; chlorambucil; cyclophosphamide; fludarabine; rituximab*; prednisolone] be balanced in terms of their adverse events in comparison to this product.
References (if required)	Debra Irwin, Kathleen Wilson, Stephen Thompson & Azhar Choudhry (2021) Real-world healthcare resource utilization and costs in patients with chronic lymphocytic leukemia: differences between patients treated with first-line ibrutinib or bendamustine + rituximab, Current Medical Research and Opinion, 37:4, 623-628, DOI: 10.1080/03007995.2021.1884540