A.15	Tyrosine kinase inhibitors – Ph+ve / BCR-ABL+ve Acute Lymphoblastic Leukemia
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: In high resource countries, the addition of agents that directly inhibit the enzymatic activity of the oncogenic fusion protein BCR/ABL to multi-agent chemotherapy regimens is standard of care in first-line treatment of Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ve / BCR-ABL+ve ALL).
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.	Currently standard chemotherapy drugs used in combination regimens (asparaginase, doxorubicin, vincristine, cytosine arabinoside, etc) are listed on the EML for ALL. It is proposed that imatinib (or potentially a later generation related TKI eg dasatinib or ponatinib) is used in combination with standard chemotherapy during induction, consolidation and maintenance phases. The purpose of the addition is to increase the cure fraction.
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 key data have been included for imatinib, but uncontrolled data for later generation ABL-inhibiting TKIs such as dasatinib and ponatinib 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 comparative cohort studies provides low quality evidence of a **major benefit in survival** for the addition of imatinib to standard chemotherapy for patients with Ph+/BCR-ABL+ve ALL. The data indicate the risk ratio for death to be 0.50 (95% CI 0.38-0.66), with 38 fewer deaths per 100 treated, and a difference in median survival of 12 months. This reflects a major improvement in outcomes for patients with this high mortality leukemia. Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?

	Imatinib has been studied in older patients and in children with low quality evidence of a similar major beneficial effect.
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Treatment of ALL has high morbidity with or without imatinib or other TKIs. The data in the application indicate a possible modest increase in cardiac toxicity, but this is very low quality evidence.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments: The toxicities of imatinib are similar to those observed with other anti-leukemia drugs.
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	The total evidence, including uncontrolled data not considered in the application, indicate a highly favourable benefit to risk ratio for imatinib. The same is likely to be true for dasatinib and for ponatinib, based on results of uncontrolled studies not included in the application.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	The overall quality of the evidence is low, but is highly consistent, and is generally recognised to indicate that imatinib provides a major survival benefit for patients with Ph+ve/BCR-ABL+ve ALL when combined with chemotherapy. The addition of TKIs to chemotherapy during induction, consolidation and as maintenance (including after allogeneic transplantation) is standard of care in high resource countries.
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: Central to the appropriate use of imatinib or any related TKI for this population is accurate identification of the presence of the predictive biomarker (Philadelphia chromosome or BCR/ABL fusion) in the ALL. The minimum standard required is FISH or metaphase cytogenetics, and complementary use of molecular tests for the BCR/ABL fusion are highly desirable. There is no evidence for general use in ALL without this genetic biomarker.
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: Imatinib, dasatinib and ponatinib are widely registered for this indication.

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: TKIs are recommended by international guidelines for this indication.
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	The price of imatinib presents the major barrier for use of this drug in low resource countries. Imatinib is now off patent, and the availability of generics has reduced prices. This should improve affordability.
Any additional comments	There are no high quality data comparing imatinib with other TKIs, however there are low quality data for imatinib, dasatinib and ponatinib that suggest each has a strong efficacy effect in the Ph+ve / BCR-ABL+ve ALL. These three TKIs do have some differences in their safety profiles, but this is a secondary consideration given the sizes of the efficacy effect size. Inclusion of one TKI on the EML is highly recommended, and price is a legitimate consideration in selecting the preferred TKI for the EML.
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.	Recommend that imatinib is included on the EML for use in adults and children with Ph+ve / BCR-ABL+ve ALL in combination with chemotherapy during induction, consolidation and maintenance. The recommendation reflects the large positive effect size on survival and the evidence of acceptable toxicity. For imatinib to be used appropriately, the diagnostic workup for newly diagnosed patients with ALL must include testing for the Ph chromosome and/or for BCR-ABL fusions. The price of imatinib presents the major barrier for use of this drug in low resource countries. Imatinib is now off patent, and the availability of generics has reduced prices. In the future, should the prices of later generation TKIs eg dasatinib or ponatinib become competitive with generic imatinib, then they should also be considered for listing on the EML.
References (if required)	