I.15	**Inclusion of Imatinib in the treatment of Philadelphia chromosome positive (Ph+) or BCR-ABL positive (BCR-ABL+) Acute lymphoblastic Leukaemia.**

Does the application adequately address the issue of the public health need for the medicine?

☒ Yes

☐ No

☐ Not applicable

Comments:

Ph+ ALL is less then 5% of ALL in children. The incidence increases to 40% in adults 40 years or greater with a 10% increment for every further decade of life.

There is no sex difference.

Prior to introduction of tyrosine kinase inhibitors (TKIs) Ph+ ALL had a poor prognosis. The5-year survival was then 10-20% with a median survival of 16 months with conventional chemotherapy.

TKIs have revolutionised the treatment for chronic myeloid leukemia including patients in blast crisis.

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.

Meta-analysis has shown that the addition of Imatinib improves survivals RR is 0.50

		Anticipated absolute effect		
Outcomes	Relative effect (CI 95%)	With TKI	Without TKI	Difference (CI 95%)
Mortality 8 studies (n = 675)	RR 0.50 (0.38 – 0.66)	38 per 100	76 per 100	38 fewer (from 26 to 47 fewer)

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).

All evidence including overall survival, progression free survival and mortality are included.

Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?

YES

<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:</td></tr>
<tr><td>Are there any adverse effects of concern, or that may require special monitoring?</td><td>☒ Yes
☐ No
☐ Not applicable
Comments:
Imatinib does not have major significant side effects if monitor properly. It is easily administered.
1. Patients with moderate renal impairment (CrCL=20-39 mL/min should receive a 50% decrease in the recommended starting dose.
2. 25% decrease in the recommended dose should be used for patients with severe hepatic impairment.
3. Rare cardiac toxicity
4. hematologic toxicities in neutropenia.</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><table><tr><td>Survival outcomes Ph+ ALL</td><td>Imatinib + chemotherapy</td><td>Chemotherapy alone</td><td>Difference</td></tr><tr><td>Overall survival (years)</td><td>4.37</td><td>1.1</td><td>+3.27</td></tr><tr><td>Disease free survival (years)</td><td>2.79</td><td>0.76</td><td>+2.04</td></tr></table>
The benefit of adding imatinib is highly favourable on response rates, PFS and OS.</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>The overall quality of the evidence in all trials is high and imatinib is highly effective.
Imatinib increases overall survival by >12 months. Mortality risks ratio: 38 less deaths per 100 patients treated.<table><tr><td></td><td></td><td colspan="3">Anticipated absolute effect</td></tr><tr><td>Outcomes</td><td>Relative effect (CI 95%)</td><td>With TKI</td><td>Without TKI</td><td>Difference (CI 95%)</td></tr><tr><td>Mortality 8 studies (n = 675)</td><td>RR 0.50
(0.38 – 0.66)</td><td>38
per 100</td><td>76
per 100</td><td>38 fewer
(from 26 to 47 fewer)</td></tr></table></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:
CBC
Ph+ ALL diagnosed by bone marrow/ flowcytometry on peripheral blood.
Cytogenetic 9:22 translocation, PCR or FISH.
Liver function
Renal function</td></tr>
</table>

<table>
<tr><td>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)</td><td>☐ Yes
☒ No
☐ Not applicable
Comments:</td></tr>
<tr><td>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)</td><td>☒ Yes
☐ No
☐ Not applicable
Comments:</td></tr>
<tr><td>Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.</td><td>Patient access programs for imatinib are available in most low middle income countries. Generic form of imatinib is available and effective.

<table><tr><td>Quality of Life</td><td>Imatinib + chemotherapy</td><td>Chemotherapy alone</td><td>Difference</td></tr><tr><td>QALYs</td><td>3.33</td><td>0.85</td><td>+2.47</td></tr></table></td></tr>
<tr><td>Any additional comments</td><td></td></tr>
<tr><td>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.</td><td><u>IMATINIB ALONE should be APPROVED for the EML & EMLc list for treatment of Ph+ ALL</u> based on evidence of relative improvement in overall survival by over 3 years and disease-free survival is improved by 2 years. Imatinib also significantly reduces risk of death and has an acceptable safety profile.
1.Imatinib is off patent now. Generics are also available
2.Available data for other TKIs (Disatinib and ponatinib) are less mature. Little evidence to support their use in children. Global availability of generics is more limited. Therefore, does not support the inclusion of TKIs as a therapeutic class at this time.</td></tr>
<tr><td>References
(if required)</td><td></td></tr>
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