# Imatinib

Essential medicine status

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.2. Targeted therapies

EMLc | ATC codes: L01EA01

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| **Indication** | B lymphoblastic leukaemia or lymphoma with t(9:22) (q34;q11.2); BCR-ABL1<br>ICD11 code: 2A70.1 |
| **INN** | Imatinib |
| **Medicine type** | Chemical agent |
| **List type** | Complementary (EML)<br>(EMLc) |
| **Formulations** | Oral > Solid: 100 mg ; 400 mg |
| **EML status history** | First added in 2021 (TRS 1035) |
| **Sex** | All |
| **Age** | Also recommended for children |
| **Therapeutic alternatives** | The recommendation is for this specific medicine |
| **Patent information** | Patents have expired in most jurisdictions<br>Read more about patents. |
| **Tags** | Cancer |
| **Wikipedia** | Imatinib |
| **DrugBank** | Imatinib |

## Expert Committee recommendation

The Expert Committee noted that Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia is the most frequent genetic subtype of acute lymphoblastic leukaemia in adults and historically has been associated with poor outcomes. The Committee acknowledged that the 5-year survival of adult patients with Ph+ acute lymphoblastic leukaemia with conventional chemotherapy was 10–20%, with a median survival of about 16 months. The addition of imatinib to conventional chemotherapy has halved the risk of premature death to around 50% and is now considered the standard of care for first-line treatment of Ph+ acute lymphoblastic leukaemia. The Committee considered the results of the meta-analysis of comparative cohort studies included in the application, which indicated a difference in median survival of 12 months with the addition of imatinib to standard chemotherapy in the treatment of acute lymphoblastic leukaemia, based on low-quality evidence. The Committee considered this to represent a highly relevant improvement in clinical benefit. The Committee considered that the safety profile of imatinib is well known and generally acceptable, and that imatinib is already listed in the EML for chronic myeloid leukaemia and gastrointestinal stromal tumour. The Committee took into account that accurate identification of the presence of the predictive biomarker (Ph+ or BCR/ABL fusion gene) requires complex tests and is central to the appropriate use of any tyrosine kinase inhibitor in acute lymphoblastic leukaemia. The Expert Committee therefore recommended the inclusion of imatinib on the EML for the treatment of adults with Ph+ acute lymphoblastic leukaemia, considering the overall survival benefit, acceptable safety profile, and that imatinib is off-patent and generic brands are becoming widely available. Noting the benefits of imatinib for paediatric patients with Ph+ acute lymphoblastic leukaemia, the Committee also extended the recommendation to inclusion on EMLc. The Committee considered that other tyrosine kinase inhibitors (e.g. dasatinib, ponatinib) might have also have a place in the treatment of Ph+ acute lymphoblastic leukaemia but that currently, data were less mature. The Committee therefore did not support the inclusion of other tyrosine kinase inhibitors within the therapeutic class at this time but would welcome a future application when mature data

are available.

## Background

Imatinib was added to the EML in 2015 for the treatment of chronic myeloid leukaemia and gastrointestinal stromal tumour (1). It was added to the EMLc for the same indications in 2019 (2). Imatinib has not previously been considered for inclusion on the EML or EMLc for the treatment of Ph+ acute lymphoblastic leukaemia.

## Public health relevance

Acute lymphoblastic leukaemia accounts for about 15% of all leukaemias (3). While it is the most common cancer in children, it is a relatively infrequent disease in adults. Excluding the paediatric population, its incidence increases with age and most new cases are diagnosed in individuals older than 65 years (4). Before the introduction of targeted therapies, the prognosis was particularly poor, with a 5-year survival of around 10–20% (5–7). The Philadelphia chromosome is the most frequent cytogenetic abnormality in adults with acute lymphoblastic leukaemia. It is seen in about 30–40% of all cases (8). It corresponds to a translocation between the ABL-1 oncogene on chromosome 9 and a breakpoint cluster region (BCR) on chromosome 22, resulting in a fusion gene, BCR-ABL, that encodes a constitutively active tyrosine kinase (9). Before the introduction of tyrosine kinase inhibitors, the presence of the Philadelphia chromosome was associated with a significantly lower probability of remission and survival at 5 years (10).

## Benefits

The applicants performed a literature search for randomized trials and systematic reviews of tyrosine kinase inhibitors in Ph+ acute lymphoblastic leukaemia, and conducted a meta-analysis of the results. Two systematic reviews (11,12) (used to identify relevant studies) and two small randomized trials (13,14) involving imatinib were identified. No data for other tyrosine kinase inhibitors were included in the application. Randomized controlled trials A small randomized trial in 32 centres in Germany between 2002 and 2005 randomly assigned 55 elderly participants (median age 68 years) with Ph+ acute lymphoblastic leukaemia to induction therapy with either imatinib (n = 28) or age-adapted chemotherapy (n = 27) (13). However, both groups later received imatinib during the consolidation chemotherapy, making it impossible to assess the effect of imatinib treatment on clinical outcomes. Another German multicentre randomized trial conducted between 2004 and 2010 assessed the use of imatinib in Ph+ acute lymphoblastic leukaemia or lymphoid blast crisis of chronic myeloid leukaemia after allogeneic haematopoietic stem-cell transplantation (14). The trial included 57 participants who were randomized to either prophylactic imatinib after haematopoietic stem-cell transplantation (n = 26) or imatinib treatment based on detection of minimal residual disease (n = 29), again making it difficult to assess the effect of imatinib treatment. Meta-analysis of cohort studies The applicants performed a meta-analysis of eight comparative cohort studies identified from two published systematic reviews (15–22). All studies included individuals with Ph+ acute lymphoblastic leukaemia, and assessed the survival of individuals who received imatinib in addition to chemotherapy versus those who received chemotherapy alone. Typically, a proportion of participants also received an allogenic stem-cell transplantation with imatinib being used before and/or after the transplantation. Two of the studies evaluated a concurrent group (15–17) while six used data from historical patients (18–22). The meta-analysis suggested that the use imatinib may significantly reduce mortality (risk ratio (RR) 0.50, 95% confidence interval (CI) 0.38 to 0.66); with 38 fewer deaths per 100 patients treated with imatinib. Four studies reported the median survival with and without imatinib (15,18–20). From these data, it was estimated that imatinib may increase overall survival by a median of 12 months compared with chemotherapy. Despite the large effect observed, there were concerns about: the risk of bias as most studies compared imatinib with historical data; and inconsistency, given that the magnitude of effect varied, with a proportion of studies showing a modest effect. Weighting these factors, the certainty of the evidence was therefore judged as low.

## Harms

Cardiac toxicity, notably congestive heart failure, is a well known, albeit rare, adverse effect of treatment with tyrosine kinase inhibitors. Data on potential toxicity of tyrosine kinase inhibitors when used for the treatment of Ph+ acute lymphoblastic leukaemia were limited. Only two of the studies included in the meta-analysis for the application reported adverse events (15,16). Meta-analysis of data from these studies indicated that the use of imatinib might increase the risk of adverse events, mainly due to cardiac toxicity (RR 1.31, 95% CI 0.73 to 2.36). In absolute terms, this would translate in eight more adverse events per 100 patients treated. The certainty of the evidence was judged as very low.

## Additional evidence

In a separate application to the meeting of the Expert Committee, imatinib was also proposed for inclusion on the EMLc for treatment of acute lymphoblastic leukaemia in children, for which it is considered standard of care. Imatinib is included in the ALLTogether trial regimen for children and young adults with acute lymphoblastic leukaemia (23) and the EsPhALL trial regimen for children with Ph+ acute lymphoblastic leukaemia (24). Several other trials studies have shown relevant benefits of imatinib in the paediatric population, with about 20% more participants alive at 5 years compared with before the introduction of imatinib for children with Ph+ acute lymphoblastic leukaemia (25–28).

## Cost / cost effectiveness

Evidence on the cost–effectiveness of tyrosine kinase inhibitors in adults with acute lymphoblastic leukaemia is limited and does not include first-generation agents such as imatinib, which are generally more available and affordable. However, even second-generation tyrosine kinase inhibitors seem to be cost-effective (30). Importantly, the patent of imatinib expired in 2016. However, this has not led to the expected rapid introduction of generic alternatives (31) nor to a substantial price reduction: generic imatinib was introduced to the market only 8% below the price of the original and even today remains a costly medicine (32).

## WHO guidelines

WHO guidelines for the treatment of acute lymphoblastic leukaemia are not available. Clinical practice guidelines from the European Society of Medical Oncology recommend that all adults with Ph+ acute lymphoblastic leukaemia receive first-line treatment with imatinib or a second-generation tyrosine kinase inhibitor, in combination with chemotherapy (12). The National Comprehensive Cancer Network Guidelines also recommend treatment with a tyrosine kinase inhibitor in combination with multiagent chemotherapy or corticosteroids as induction treatment for Ph+ acute lymphoblastic leukaemia in adults, young adults and adolescents (29).

## Availability

Imatinib has marketing approval from multiple national regulatory agencies, including the Australian Therapeutic Goods Administration, the European Medicines Agency, Health Canada, the Japanese Pharmaceuticals and Medical Devices Agency and the United States Food and Drug Administration. It is available in branded and generic forms.

## Other considerations

The EML Cancer Medicines Working Group supported the inclusion of imatinib on both the EML and EMLc for the treatment of adults and children with Ph+ acute lymphoblastic leukaemia based on evidence of relevant improvement in survival and acceptable safety. Despite also being associated relevant survival benefit, the available data for other tyrosine kinase inhibitors (dasatinib, ponatinib) are less mature. There is little evidence supporting their use in children and their global availability (including generics) is more limited. Therefore, the Working Group did not support the inclusion of tyrosine kinase inhibitors as a therapeutic class at this time. Comments were received from the WHO Department of Noncommunicable Diseases. The technical unit considered that there is sufficient evidence to justify the inclusion of imatinib on the EML for the treatment of Ph+ acute lymphoblastic leukaemia given its clinical impact and the feasibility of its appropriate use, noting its increasing availability for other cancer-related indications. Imatinib treatment for Ph+ acute lymphoblastic leukaemia is known to reduce mortality, improve quality of life and it has a favourable safety profile. Data for other tyrosine kinase inhibitors (e.g. dasatinib, ponatinib) are less mature.

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