Application to add tyrosine kinase inhibitors to WHO Model List of Essential Medicines

As a Medicine for Treatment of Adults with Philadelphia chromosome–positive (Ph+) or BCR-ABL–positive (BCR-ABL+) Acute Lymphoblastic Leukaemia

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Potential conflicts of interest

All the authors declare no conflict of interest

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General items

1. Summary statement of the proposal for inclusion, change or deletion.

This application proposes to add tyrosine kinase inhibitors to the list of WHO Essential Medicine as treatment for adults with Philadelphia chromosome–positive (Ph+) or BCR-ABL–positive (BCR-ABL+) acute lymphoblastic leukaemia

Acute lymphoblastic leukaemia is a relatively infrequent disease in adults. However, previous to the introduction of tyrosine kinase inhibitors, the prognosis was particularly poor. The Philadelphia chromosome is the most frequent cytogenetic abnormality in adults with acute lymphoblastic leukaemia. This cytogenetic abnormality produces a fusion gene, BCR-ABL, that encodes an constitutively active tyrosine kinase. The use of drugs that can selectively block this abnormal protein has significantly changed the prognosis of the disease.

The meta-analysis of the studies identified suggested that the use imatinib may significantly reduce mortality (RR 0.50, 95% CI 0.38-0.66; 38 fewer deaths per 100 treated; low certainty evidence). With a median increase of survival of 12 months and a larger proportion of patients that can undergo to allogenic stem-cell transplantation.

Economic evidence regarding the cost-effectiveness of tyrosine kinase inhibitors in adults with acute lymphoblastic leukaemia is sparse. Also, do not include older drugs that are more generally available and affordable. However, even second-generation tyrosine kinase inhibitors seems to be cost-effective.

Importantly, the patent of imatinib, the first tyrosine kinase inhibitor, expired in 2016. However, this has not lead to the expected rapid introduction of generic alternatives[1] nor to a significant price reduction: generic imatinib was introduced to the market only 8% below the price of the original and even today remains as a costly drug.[2]

Tyrosine kinase inhibitors inaugurated an era of specialty drugs in medicine. Twenty years later, there are still important challenges to enhance the accessibility and affordability of these drugs, specially imatinib.

2. Relevant WHO technical department and focal point.

Department of Health Products Policy and Standards, World Health Organization, Geneva, Switzerland

3. Name of organization(s) consulted and/or supporting the application.

Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

WHO Collaborating Center for Evidence Informed Policy, McMaster University, Hamilton, Ontario, Canada

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

International Nonproprietary Name (INN)	Anatomical Therapeutic Chemical (ATC) code
Imatinib	L01XE01

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

Capsule or tablet: 100 mg; 400 mg

The recommended dose of imatinib is 600 mg/day for adult patients.

Patients with mild and moderate hepatic impairment do not require a dose adjustment. A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment.

Patients with moderate renal impairment (CrCL=20–39 mL/min) should receive a 50% decrease in the recommended starting dose.

Imatinib can cause fetal harm when administered to a pregnant woman based on human and animal data. There are no clinical studies regarding use of imatinib in pregnant women. Imatinib and its active metabolite are excreted into human milk.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

As individual medicine.

Treatment details, public health relevance and evidence appraisal and synthesis

7. Treatment details

Tyrosine kinase inhibitors has been used successfully in adults in the different stages of acute lymphoblastic leukemia: during the induction, the consolidation and after allogeneic stem cell transplantation.

8. Information supporting the public health relevance.

Acute lymphoblastic leukaemia is a relatively infrequent disease in adults. However, previous to the introduction of targeted therapies, the prognosis was particularly poor, with a 5-years survival around 10-20%.[3-5]

Acute lymphoblastic leukaemia accounts for approximately 15% of leukaemias.[6] Excluding the paediatric population, its incidence increases with age, and the majority of new cases are diagnosed in individuals over 65 years old.[7]

The Philadelphia chromosome is the most frequent cytogenetic abnormality in adults with acute lymphoblastic leukaemia. It can be observed in about 30% to 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 an constitutively active tyrosine kinase.[9] Previous to the introduction of tyrosine kinase inhibitors, the presence of Philadelphia chromosome was associated with a significantly lower probability of remission and survival at 5 years.[10]

9. Review of benefits: summary of evidence of comparative effectiveness.

Methods

We searched for randomized trials up to December 2020 on MEDLINE and EMBASE, from date of inception and without language limits. Additionally, we searched for up to date systematic reviews in MEDLINE, EMBASE and The Cochrane Library (see appendix). We used the systematic reviews as a way to identify relevant studies, but conducted our own meta-analysis.

We used the following inclusion criteria:

1. Study design: Randomized trials or comparative cohort study
2. Population: Individuals with Ph+ acute lymphoblastic leukaemia
3. Intervention: tyrosine kinase inhibitors
4. Comparison: any therapy without tyrosine kinase inhibitors.

We assessed the risk of bias using the Cochrane Collaboration Risk of Bias Tool. We also made judgments about precision, consistency, directness, and likelihood of publication bias following the GRADE approach.

We meta-analyzed the data using the Mantel–Haenszel method, random effect model. We assessed heterogeneity with the Chi-square test and with the I2 statistic. All the meta-analyses were conducted using RevMan (Version 5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

We identified 2 systematic reviews[11,12] and 2 small randomized trials.[13,14]

The first trial identified was conducted in elderly patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia.[13] Participants were randomized to induction therapy with either imatinib or age-adapted chemotherapy. However, both groups later received imatinib during the consolidation chemotherapy.

The second trial identified assessed the use of imatinib in Philadelphia chromosome-positive acute lymphoblastic leukaemia or lymphoid blast crisis of chronic myeloid leukaemia after

allogeneic stem cell transplantation.[14] Therefore, it was also considered not relevant to the question of interest.

Through the systematic reviews retrieved, we identified 8 additional comparative cohort studies.[15-22] All of them included individuals with Philadelphia chromosome-positive acute lymphoblastic leukaemia. In all the studies, investigators explored the prognosis 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. Imatinib was used before and/or after allogenic stem-cell transplantation. Regarding the control group, 2 of the studies evaluated a concurrent group,[15-17] while 6 used data from historical patients.[18-22]

The meta-analysis of the studies identified suggested that the use imatinib may significantly reduce mortality: RR 0.50, 95% CI 0.38-0.66; 38 fewer deaths per 100 treated; low certainty evidence. Four studied reported the median survival with and without imatinib.[15,18-20] From this data, we estimated that imatinib may increase overall survival in 12 more months (median difference).

Given the large effect observed, we considered upgrading the certainty of the evidence to moderate. However, there were concerns regarding the risk of bias – most studies compared imatinib with historical data; and inconsistency, given that an important proportion of studies did not suggest a large effect. Weighting all these factors, we judged the certainty of the evidence as low.

Summary of Potential Benefits

Outcomes	Relative Effect (CI 95%)	Anticipated absolute effect			Certainty of the Evidence (GRADE)
		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)	⨁⨁◯◯[a, b] **LOW**

Abbreviations: RR: Risk ratio; CI: Confidence interval; TKI: Tyrosine Kinase Inhibitors.

a. Evidence from observational studies. There are serious concerns regarding the risk of confounding, since the majority of the evidence comes from comparisons with historical controls. Additionally, there

was no adjusted analysis available in the majority of the studies. Therefore, we rated down the certainty of the evidence from high to low.

b. We considered an upgrade of the certainty of the evidence given the large effect of the intervention. However, we observed substantial heterogeneity on the meta-analysis, with a proportion of studies suggesting a smaller effect.

10. Review of harms and toxicity: summary of evidence of safety.

The data regarding potential toxicity of tyrosine kinase inhibitors is sparse. In the studies identified, only 2 reported adverse events.[15,16]

According to the data identified, the use of tyrosine kinase inhibitors might increase the risk of adverse events, mainly due to cardiac toxicity (RR 1.31, 95% CI 0.73 - 2.36; 8 more adverse events per 100 treated; very-low certainty evidence).

Summary of Potential Harms

Outcomes	Relative Effect (CI 95%)	Anticipated absolute effect			Certainty of the Evidence (GRADE)
		WITH TKI	WITHOUT TKI	Difference (CI 95%)	
Adverse events 2 studies (n=126)	**RR 1.31** (0.73 - 2.36)	**35** per 100	**27** per 100	**8 more** (from 7 fewer to 37 more)	⨁◯◯◯[a, b] **VERY LOW**

Abbreviations: RR: Risk ratio; CI: Confidence interval; TKI: Tyrosine Kinase Inhibitors.

a. Evidence from observational studies. There are serious concerns regarding the risk of confounding due the lack of adjusted analysis available in the majority of the studies. Therefore, we rated down the certainty of the evidence from high to low

b. Additionally we rated down the certainty of the evidence due to imprecision, given the small number of events and the amplitude of the confidence intervals.

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

Methods

We searched for economic evaluations up to December 2020 on MEDLINE, EMBASE and the Cochrane library (see appendix). Additionally, we hand-searched the websites of the following agencies and organizations: The National Institute of Health Research, The Centre of Review and Dissemination, The Canadian Agency for Drugs and Technologies in Health (CADTH), The National Institute for Health and Care Excellence (NICE), Pharmaceutical Benefits Advisory Committee (PBAC) and The International Network of Agencies for Health Technology Assessment (INHATA).

Inclusion/exclusion

Inclusion

We included full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population.

Exclusion

We excluded studies that only reported cost per hospital (not per patient), or only reported average cost-effectiveness without disaggregated costs and effects. Also we excluded abstracts, posters, reviews, letters/editorials, and unpublished studies

Results

We identified only one study and one agency report. The study was cost-utility assessment from the UK health and social perspective.[23] The model used a state transition for patients previously treated Philadelphia-chromosome-positive acute lymphoblastic leukemia, comparing ponatinib against re-induction of chemotherapy and best supportive care (BSC) in patients who were not candidates for other tyrosine kinase inhibitors. The final values for the base-case ICERs were: £26,319 per QALY gained compared with best supportive care (BSC), and £29,812 per QALY gained compared with re-induction chemotherapy for patients suitable

for allogeneic stem cell transplant. Considering the usual threshold of willingness to pay of £30,000 used in UK, ponatinib was judged likely as a cost-effective alternative.

One agency, The National Institute for Health and Care Excellence (NICE, https://www.nice.org.uk; UK), published a report evaluating ponatinib based on the study described. They recommended covering the medication in specific subgroups of patients and with a price discount that is secret to public.

Summary of Economic Evaluations

Study	Limitations	Other comments		Cost-effectiveness (ICER)	Uncertainty
Stevenson M. 2018 [23]	potentially serious limitations [a]	Model	State transition model with 3-monthly time cycles and includes a half-cycle correction	Incremental cost-effectiveness ratio (ICER) for ponatinib was £26,624 per quality-adjusted life-year (QALY) gained compared with BSC and £31,123 per QALY gained compared with re-induction chemotherapy. During the appraisal, the company agreed to a commercial-in-confidence discount. This resulted in base-case ICERs estimated by the company of £26,319 per QALY gained compared with BSC and was £29,812 per QALY gained compared with re-induction chemotherapy for patients suitable for allo-SCT.	The AC recognised that there was considerable uncertainty in the value of the ICERs, and therefore their most likely value fell within a range. The AC concluded that, in all instances, this range included cost-effective values, and therefore ponatinib was a cost-effective use of NHS resources.
		Population	Ph+ ALL in patients whose disease is resistant to dasatinib, who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate or who have the threonine-315-isoleucine mutation		
		Time horizon	Lifetime horizon		
		costs	Costs included medication, human health resource, routine physician follow-up, hospitalization and laboratory investigations. The cost of ponatinib was stated to be commercial-in-confidence because of the PAS and the dosing regimens observed in PACE.		
		Utilities	Patients who responded to treatment were assumed to have a utility decrement of 0.286, and patients who did not respond to treatment had a utility decrement of 0.556 compared with the general population. Patients who received allo-SCT were assumed to have a utility decrement that reduced over time, being 0.296 within the first 3 months 0.136 after 6 months and assumed to be 0.216 between 3 and 6 months. The utilities for all adverse events were assumed to be 0.52		
		Perspective	UK health and social system		
		Others	Both benefits and costs were discounted at a rate of 3.5% per annum		

Abbreviations: Philadelphia-chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL), best supportive care (BSC), low-dose chemotherapy (LDC) standard-dose chemotherapy (SDC), allogeneic stem cell transplant (allo-SCT), Quality-adjusted life year (QALY). incremental cost-effectiveness ratios (ICERs), patient access scheme (PAS), the NICE appraisal committee (AC)

a. There was uncertainty in the economic modelling because of the indirect comparison of evidence.

Regulatory information

12. Summary of regulatory status and market availability of the medicine.

US Food and Drug Administration: Approved

European Medicines Agency: Approved

Australian Government: Approved

Japanese Pharmaceuticals and Medical Devices Agency: Approved

Health Canada: Approved

13. Availability of pharmacopoeial standards

Imatinib, Dasatinib and Ponatinib

International Pharmacopoeia: No

British Pharmacopoeia: No

European Pharmacopoeia: No

United States Pharmacopoeia: No

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Appendix

Appendix 1: Search strategies

Search strategy for randomized trials in MEDLINE and EMBASE (via OVID)
DATE: December 2020

1. exp Protein Kinase Inhibitors/
2. Protein Kinase Inhibitors.mp.
3. exp Dasatinib/
4. exp Imatinib Mesylate/
5. Ponatinib.mp.
6. Nilotinib.mp.
7. exp Precursor Cell Lymphoblastic Leukemia-Lymphoma/
8. Acute lymphoblastic leukemia.mp.
9. Ph+ ALL.mp.
10. randomized controlled trial.pt.
11. controlled clinical trial.pt.
12. randomi?ed.ab.
13. placebo.ab.
14. drug therapy.fs.
15. randomly.ab.
16. trial.ab.
17. groups.ab.
18. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. exp animals/ not humans.sh.
20. 18 not 19
21. 1 or 2 or 3 or 4 or 5 or 6
22. 7 or 8 or 9
23. 20 and 21 and 22

Search strategy for systematic reviews in MEDLINE and EMBASE (via OVID)
DATE: December 2020

1. exp Protein Kinase Inhibitors/
2. Protein Kinase Inhibitors.mp.
3. exp Dasatinib/
4. exp Imatinib Mesylate/
5. Ponatinib.mp.
6. Nilotinib.mp.
7. exp Precursor Cell Lymphoblastic Leukemia-Lymphoma/
8. Acute lymphoblastic leukemia.mp.
9. Ph+ ALL.mp.
10. systematic review/
11. meta-analysis/
12. (meta analy* or metanaly* or metaanaly*).ti,ab.
13. ((systematic or evidence) adj2 (review* or overview*)).ti,ab.
14. (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
15. (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
16. cochrane.jw.
17. 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 1 or 2 or 3 or 4 or 5 or 6
19. 7 or 8 or 9
20. 17 and 18 and 19

Search strategy for economic evaluations in MEDLINE (via OVID)
DATE: December 2020

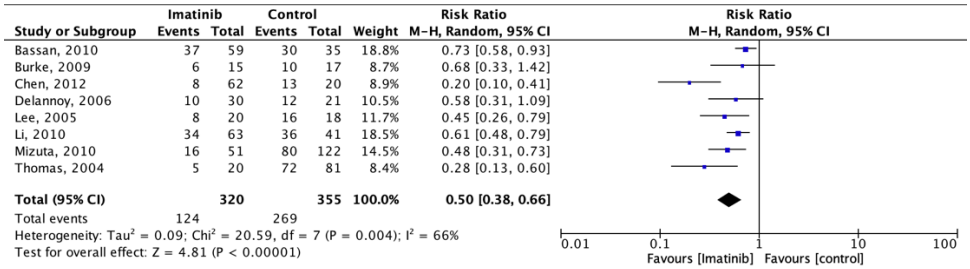
("protein kinase inhibitors"[MeSH Terms] OR “tyrosine kinase inhibitors” OR “tyrosine kinase protein” OR “Protein kinase inhibitors” OR dasatinib OR imatinib OR Volasertib OR PKI-587 OR Idelalisib OR BEZ235 OR ABL001 OR Dasatinib OR Ponatinib OR Gefitinib OR T315I OR MK-2206 OR GSK690693 OR Pimasertib OR Ciclopirox OR AZD8055 OR Sirolimus OR Temsirolimus OR Everolimus OR Pacritinib OR Ruxolitinib OR Acalabrutinib OR Ibrutinib OR Bortezomib OR Crenolanib OR Gilteritinib OR Tandutinib OR Lestaurtinib OR Sunitinib OR Midostaurin OR Quizartinib) AND (“acute leukemia” OR “Acute lymphocytic leukaemia” OR “Lymphocytic Leukemia, Acute” OR acute lymphoblastic leukemia[MeSH Terms] OR “acute lymphoblastic leukemia”) AND (Economics[Mesh:NoExp] OR "Cost-Benefit Analysis"[Mesh] OR "Costs and Cost Analysis"[mh] OR Economics, Nursing[mh] OR Economics, Medical[mh] OR Economics, Pharmaceutical[mh] OR Economics, Hospital[mh] OR Economics, Dental[mh] OR "Fees and Charges"[mh] OR Budgets[mh] OR budget*[tiab] OR economic*[tiab] OR cost[tiab] OR costs[tiab] OR costly[tiab] OR costing[tiab] OR price[tiab] OR prices[tiab] OR pricing[tiab] OR pharmacoeconomic*[tiab] OR pharmaco-economic*[tiab] OR expenditure[tiab] OR expenditures[tiab] OR expense[tiab] OR expenses[tiab] OR financial[tiab] OR finance[tiab] OR finances[tiab] OR financed[tiab] OR value for money[tiab] OR monetary value*[tiab] OR models, economic[mh] OR economic model*[tiab] OR markov chains[mh] OR markov[tiab] OR monte carlo method[mh] OR monte carlo[tiab] OR Decision Theory[mh] OR decision tree*[tiab] OR decision analy*[tiab] OR decision model*[tiab] OR “Single Technology Appraisal”OR “HTA” OR “Technology Appraisal”)

Search strategy for economic evaluations in EMBASE (via OVID)
DATE: December 2020

(acute lymphoblastic leukemia/ OR acute lymphoblastic leukaemia.mp. [mp=hw, ab, ti, ct, sh, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]) AND
((protein tyrosine kinase inhibitor/) OR (dasatinib or imatinib or Volasertib or PKI-587 or Idelalisib or BEZ235 or ABL001 or Dasatinib or Ponatinib or Gefitinib or T315I or MK-2206 or GSK690693 or Pimasertib or Ciclopirox or AZD8055 or Sirolimus or Temsirolimus or Everolimus or Pacritinib or Ruxolitinib or Acalabrutinib or Ibrutinib or Bortezomib or Crenolanib or Gilteritinib or Tandutinib or Lestaurtinib or Sunitinib or Midostaurin or Quizartinib).mp. [mp=hw, ab, ti, ct, sh, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]))
AND (Cost-effectiveness.mp. or "cost utility analysis"/ or "cost benefit analysis"/ or "cost minimization analysis"/ or "cost"/ or "cost effectiveness analysis"/ or QALY.mp. or quality adjusted life year/ or health technology assessment.mp. or biomedical technology assessment/ or economics/ or willingness to pay.mp. or "health care cost"/ or life years gained.mp. or disability-adjusted life years.mp. or disability-adjusted life year/ or Statistical Model/ or economic model*.ab,ti. or Probability/ or markov.ti,ab,kw. or monte carlo method/ or monte carlo.ti,ab. or Decision Theory/ or Decision Tree/ or health technology assessment.mp.) AND (acute lymphoblastic leukemia/)

Appendix 2: Forest plots

Tyrosine kinase inhibitors - Mortality.



Tyrosine kinase inhibitors - Adverse effects: cardiac toxicity