

ATC codes: **L01EL01**

ICD11 code: **2B52.0**

Indication	Chronic lymphocytic leukaemia or small lymphocytic lymphoma
INN	Ibrutinib
Medicine type	Chemical agent
List type	Complementary
Formulations	Oral > Solid: 140 mg
EML status history	First added in 2021 (TRS 1035)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents .


Tags

Cancer

Wikipedia

[Ibrutinib](#) 

DrugBank

[Ibrutinib](#) 

Expert Committee recommendation

The Committee noted that targeted therapy with Bruton tyrosine kinase inhibitors, such as ibrutinib, was now emerging as the cornerstone of CLL treatment in high-income countries, replacing chemoimmunotherapy as the accepted standard of care because such therapy is more effective, has less acute toxicity and a minimal risk of development of secondary leukaemias. The Committee considered the results of the meta-analysis presented in the application which covered all patients with CLL, and which showed with moderate-certainty evidence that ibrutinib increased overall survival, and with high-certainty evidence that ibrutinib increased progression-free survival. The trials included in the meta-analysis were in both the first-line and relapsed/refractory settings, and in both settings, ibrutinib was consistently associated with highly relevant clinical benefits. The Committee noted that in relapsed/refractory patients, the data were more mature (6 years of follow-up), with ibrutinib showing significantly longer overall survival and progression-free survival than immunotherapy with the anti-CD20 monoclonal antibody ofatumumab, including in patients with high-risk disease features such as 17p deletion or other genetic mutations associated with poor prognosis. In the first-line treatment setting, the available data are less mature (3 years of follow-up), but they also demonstrate benefit in terms of progression-free survival and response rates of ibrutinib compared with chemoimmunotherapy, including in patients with high-risk disease features. In absolute terms, the use of ibrutinib prolongs progression-free survival by at least 50 months compared with chemoimmunotherapy, with the effect being relatively uniform and robust in both first- and later-line settings. However, the quality of evidence supporting the use of ibrutinib in the subgroup of patients with CLL with 17p deletion is not as complete as it is for the whole population of patients with relapsed/refractory CLL and is immature for treatment-naïve patients. With regard to safety, the Committee noted the significant cardiovascular toxicity associated with ibrutinib, particularly atrial fibrillation and hypertension. Most patients who start ibrutinib for CLL will remain on this drug for many years as treatment is usually continued until disease progression. Monitoring and management of these side-effects require considerable resources. Major bleeding is also seen in some

patients, for which specialized care and resources are required for management. The Committee considered that the data in the relapsed/refractory setting were compelling for a major sustained benefit and improved tolerability for all patients with CLL (with or without 17p deletion). Therefore, the Committee recommended the inclusion of ibrutinib on the complementary list of the EML for the treatment of relapsed/refractory CLL. The Committee acknowledged the potential role for ibrutinib as first-line treatment, particularly in the subgroup of patients with CLL with 17p deletion, but considered that the available evidence, while promising, was currently immature unlike the evidence for relapsed/refractory disease. The Committee therefore did not recommend listing ibrutinib for first-line treatment at this time. The Committee requested that an application be submitted for consideration at the next Expert Committee meeting when more mature data on ibrutinib for first-line treatment will be available. The Committee noted that ibrutinib was not found to be cost-effective at current prices in multiple analyses, particularly when used in first-line treatment for all patients. The Committee recognized the very high price of ibrutinib (tens of thousands of US\$ per year in many settings), and the long duration of the treatment, which will have a significant financial impact on individuals and health systems. The increasing availability of other Bruton tyrosine kinase inhibitors and the availability of generics of ibrutinib reported in a few countries were also noted, and it was expected that these factors would introduce competition to reduce prices. Nevertheless, the Committee recognized that the current price of ibrutinib was prohibitive for most low- and middle-income countries. The Committee also considered that the lack of access to molecular testing to identify CLL patients with chromosome 17p deletion may be a limitation in some resource-constrained settings. Therefore, the Committee did not limit ibrutinib treatment to this subgroup when making its recommendation. The Committee recommended that ibrutinib be flagged to the Medicines Patent Pool as a candidate for negotiating public health-oriented licences with the patent-holding companies to facilitate more affordable access to ibrutinib in low- and middle-income countries. In addition, the Committee considered that ibrutinib would be a potential candidate for WHO prequalification to facilitate access to affordable and quality-assured products. The Committee therefore requested the WHO Prequalification Programme consider the inclusion of ibrutinib in its invitation for expressions of interest to manufacturers, so that ibrutinib can be eligible for prequalification. Finally, recognizing the emerging important role of Bruton tyrosine kinase inhibitors as a therapeutic class in first- and second-line treatment of CLL, the Committee advised that it would welcome an application including other Bruton kinase inhibitors (e.g. acalabrutinib, zanubrutinib) for consideration as therapeutic alternatives for inclusion on the EML in the future.

Background

Ibrutinib has not previously been considered for inclusion on the EML. Medicines currently included on the EML for CLL are bendamustine, chlorambucil, cyclophosphamide, fludarabine, prednisolone and rituximab, recommended for inclusion as part of the comprehensive review of cancer medicines undertaken by the Expert Committee in 2015 (1). Ibrutinib belongs to the class of Bruton tyrosine kinase inhibitors which are currently not listed on the EML for any indication. Continuous activation of Bruton tyrosine kinase plays an important role in the proliferation of malignant B-cells, which can be counteracted by Bruton tyrosine kinase inhibitors.

Public health relevance

CLL is the most common form of adult leukaemia in many high-income countries and its incidence increases significantly with age (2). Its incidence in Australia, North America and some European countries is considerably higher than in Asian and Central and South American countries. Age-adjusted incidence rates range from 0.1 per 100 000 people in Japan for both males and females, to 2.4 per 1000 000 for females and 4.5 per 100 000 for males in Canada (3). Globally, the absolute number of deaths due to CLL increased by 70% from 1990 to 2017. Of note, the age-adjusted death rates have decreased in high-income regions, largely due to access to and availability of effective treatments, but have increased in many lower-income settings where effective treatment is not available or affordable (4). Since CLL is a slowly progressing disease, patients with early-stage asymptomatic disease usually do not require treatment. In patients with more advanced and symptomatic disease, the aim of treatment is to improve the quality of life and prolong survival since for now, with few exceptions, CLL cannot be cured. Patients with CLL with chromosome 17p deletion are a high-risk subgroup whose disease is refractory to chemoimmunotherapy with the treatments currently included on the EML, and whose prognosis is very poor. CLL with 17p deletion accounts for than 10% of new cases, and 30–50% of relapsed/refractory cases previously treated with chemoimmunotherapy (5). Ibrutinib appears to benefit in this subgroup of patients. The economic burden of CLL on both patients and health systems is substantial. Annual direct costs per person with CLL have been estimated to range between US\$ 4500 in Germany and US\$ 44 000 in the United States of America (6).

Benefits

Four systematic reviews (7–10) and five randomized trials (11–15) assessing ibrutinib for the treatment of CLL were identified in the application. Two of these trials were direct comparisons of ibrutinib with another targeted therapy not included on the EML (another Bruton tyrosine kinase inhibitor in one study and an anti-CD20 monoclonal antibody in the other) and were therefore not included in the meta-analysis conducted by the applicants (11,15). The remaining three trials provided data on the effect of ibrutinib as a first- or second-line of treatment in patients with CLL. Two trials were conducted in treatment-naïve patients. One compared ibrutinib with chlorambucil for 12 cycles in patients without the 17p deletion (12), while the other trial evaluated ibrutinib plus obinutuzumab (an anti-CD20 monoclonal antibody) versus chlorambucil plus obinutuzumab for six cycles (13). This trial included participants with 17p deletion, although they represented only a small proportion of the participants included (about 14%). The third trial enrolled participants with relapsed/refractory disease and assessed the effect of ibrutinib plus bendamustine and rituximab versus bendamustine plus rituximab alone. Participants with the 17p deletion were excluded from this study due to the known poor response of these patients to bendamustine plus rituximab (14). A meta-analysis of these three studies showed that the use of ibrutinib as a first- or second-line treatment probably increases progression-free survival (hazard ratio (HR) 0.20, 95% confidence interval (CI) 0.14 to 0.27; high-certainty evidence) and probably also overall survival (HR 0.44, 95% CI 0.20 to 0.97; moderate-certainty evidence). Median overall survival had not been reached. Median progression-free survival was reached in one trial of patients with relapsed/refractory disease (14), and indicated a progression-free survival gain of 50.8 months in absolute terms. One trial reported the effect of ibrutinib on quality of life and found that the use of ibrutinib resulted in a statistically significant improvement in scores of the Functional Assessment of Chronic Illness Therapy (FACIT) – Fatigue and the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) questionnaires. The mean difference observed in the FACIT – Fatigue score was 2.6 points (95% CI 0.4 to 4.9 points); however, this is below the minimally important differences reported for this scale (16). In addition, the mean difference reported in the physical functioning score of EORTC QLQ-C30 was 5.0 points (95% CI 0.75 to 9.25 points), which is also under the reported minimal important difference for this domain (17).

Harms

Only one of the included trials reported adverse events in both treatment groups (13). For the comparison of ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab, the frequency of grade 3 and 4 adverse events was similar in both arms (risk ratio (RR) 0.98, 95% CI 0.82 to 1.17; low-certainty evidence). Common adverse events associated with ibrutinib included neutropenia, pneumonia, hypertension, anaemia, hyponatremia and atrial fibrillation. However, systematic reviews have linked the use of ibrutinib with an increased risk of hypertension, atrial fibrillation and major bleeding (9,10). The use of ibrutinib (in comparison with regimens without ibrutinib) probably results in 60 more cases of hypertension (95% CI 20 to 160 more; moderate-certainty evidence), 19 more cases of atrial fibrillation (95% CI 10 to 58 more; high-certainty evidence) and 122 more bleeding events (95% CI –8 fewer to 370 more; moderate-certainty evidence) per 1000 patients treated.

Cost / cost effectiveness

Three studies that evaluated the cost-effectiveness of ibrutinib for treatment of CLL/small lymphocytic lymphoma were identified in the application (18–20). One study was a cost-utility analysis from the Swedish health system perspective in a population of patients with refractory or relapsed CLL (18). The authors concluded that ibrutinib could be cost-effective compared with ofatumumab, idelalisib plus ofatumumab or physicians' choice of treatment. However, the incremental cost-effectiveness ratios were around € 60 000 per quality-adjusted life-year (QALY) gained, higher than the thresholds most often used in European countries. A cost-utility analysis from the United States Medicare perspective was done using ibrutinib as first-line therapy versus obinutuzumab and chlorambucil (19). In a cohort of patients older than 65 years without the 17p deletion, the incremental cost-effectiveness ratios was US\$ 189 326 per QALY gained, showing that ibrutinib was not a cost-effective alternative at the current price and willingness-to-pay thresholds. The third study was a cost-utility analysis from the perspective of the National Health System of the United Kingdom of Great Britain and Northern Ireland in adults with untreated CLL. The model compared ibrutinib with obinutuzumab plus chlorambucil and showed an incremental cost-effectiveness ratio of £ 75 648 per QALY gained, which is more than the commonly used willingness-to-pay thresholds used in the United Kingdom of £ 20 000–30 000 per QALY gained used by the National Institute for Health and Care Excellence for new treatments, and of £ 50 000 per QALY gained for end-of-life

treatments (20). The applicants report that national reimbursement agencies in Australia, Canada and the United Kingdom have evaluated the cost-effectiveness of ibrutinib and recommended coverage, albeit in specific subgroups of patients and under confidential pricing agreements.

WHO guidelines

WHO guidelines for the treatment of CLL are not available.

Availability

Ibrutinib 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. Ibrutinib is under patent until 2027. However, generics are available in some countries.

Other considerations

The EML Cancer Medicines Working Group advised that it supported the inclusion of ibrutinib on the EML as first-line treatment for the high-risk subgroup of patients with CLL with 17p deletion, recognizing that this population has a significantly poorer prognosis, and an unmet need for effective treatment exists. A broader role for ibrutinib in all patients with CLL, and in the second-line setting, is not supported at this time. However, the Working Group noted the significant cardiovascular toxicity associated with ibrutinib, in particular atrial fibrillation and major bleeding, management of which requires specialized care and resources that may not be widely available in some settings. The Working Group also considered that the need for molecular testing to identify patients with 17p deletion, who are most likely to benefit from treatment, may be a further limitation, particularly in some resource-constrained settings where such testing may not be available or affordable. The Working Group also recognized the high cost of the medicine, the potentially long duration of treatment and the fact that ibrutinib has not been found to be cost-effective at current prices in multiple analyses. It is hoped that with the emerging availability of generics in some settings, the price will decrease and treatment will be more affordable. Comments were received from the WHO Department of Noncommunicable Diseases. The technical department advised that at the current time, there was not a strong justification for inclusion of ibrutinib on the EML. The department acknowledged that CLL with 17p/TP53 deletion could be a specific indication for which ibrutinib may have merit; however, given the important health system requirements, including the need for complex diagnostic tests (to avoid inappropriate prescribing and use), the high risk of clinically relevant side-effects, and the absence of an improvement in quality of life, the technical department concluded that there were currently insufficient data to merit its inclusion. The technical department also noted that more data on the clinical benefit of ibrutinib for the treatment of patients with CLL with 17p/TP53 deletion would be valuable to better evaluate its potential role as an essential medicine.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2015. (WHO Technical Report Series, No. 994; <https://apps.who.int/iris/handle/10665/189763>, accessed 8 June 2021).
2. Redaelli A, Laskin BL, Stephens JM, Botteman MF, Pashos CL. The clinical and epidemiological burden of chronic lymphocytic leukemia. *Eur J Cancer Care (Engl)*. 2004;13(3):279–87.
3. Miranda-Filho A, Piñeros M, Ferlay J, Soerjomataram I, Monnereau A, Bray F. Epidemiological patterns of leukaemia in 184 countries: a population-based study. *The Lancet Haematology*. 2018;5(1):e14–e24.
4. Ou Z, Yu D, Liang Y, He W, Li Y, Zhang M, et al. Analysis of the Global Burden of Disease study highlights the trends in death and disability-adjusted life years of leukemia from 1990 to 2017. *Cancer Commun (Lond)*. 2020;40(11):598–610.
5. Zenz T, Gribben JG, Hallek M, Döhner H, Keating MJ, Stilgenbauer S. Risk categories and refractory CLL in the era of chemoimmunotherapy. *Blood*. 2012;119(18):4101–7.
6. Frey S, Blankart CR, Stargardt T. Economic burden and quality-of-life effects of chronic lymphocytic leukemia: a systematic review of the literature. *Pharmacoeconomics*. 2016;34(5):479–98.
7. Molica S, Giannarelli D, Baumann T, Montserrat E. Ibrutinib as initial therapy in chronic lymphocytic leukemia: a systematic review and meta-analysis. *Eur J Haematol*. 2020;104(5):512–5.
8. Puła A, Stawiski K, Braun M, Iskierka-Jażdżewska E, Robak T. Efficacy and safety of B-cell receptor signaling pathway inhibitors in relapsed/refractory chronic lymphocytic leukemia: a systematic review and meta-analysis of randomized clinical trials. *Leuk Lymphoma*. 2018;59(5):1084–94.
9. Caldeira D, Alves D, Costa J, Ferreira JJ, Pinto FJ. Ibrutinib increases the risk of hypertension and atrial fibrillation: systematic review and meta-analysis. *PLoS One*. 2019;14(2):e0211228.
10. Caron F, Leong DP, Hillis C, Fraser G, Siegal D. Current understanding of bleeding with ibrutinib use: a systematic review and meta-analysis. *Blood Adv*. 2017;1(12):772–8.
11. Munir T, Brown JR, O'Brien S, Barrientos JC, Barr PM, Reddy NM, et al. Final analysis from RESONATE: up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol*. 2019;94(12):1353–63.
12. Burger JA, Tedeschi A, Barr PM, Robak T, Owen C, Ghia P, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373(25):2425–37.

13. Moreno C, Greil R, Demirkan F, Tedeschi A, Anz B, Larratt L, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 2019;20(1):43–56.
14. Fraser GAM, Chanan-Khan A, Demirkan F, Santucci Silva R, Grosicki S, Janssens A, et al. Final 5-year findings from the phase 3 HEALIOS study of ibrutinib plus bendamustine and rituximab in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. *Leuk Lymphoma.* 2020;61(13):3188–97.
15. Hillmen P, Brown JR, Byrd JC, Eichhorst B, Lamanna N, O'Brien SM, et al. ALPINE: Phase III zanubrutinib (BGB-3111) versus ibrutinib in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). *J Clin Oncol.* 2019;37(15 Suppl):TPS7572–TPS.
16. Nordin Å, Taft C, Lundgren-Nilsson Å, Dencker A. Minimal important differences for fatigue patient reported outcome measures—a systematic review. *BMC Med Res Methodol.* 2016;16:62.
17. Jayadevappa R, Cook R, Chhatre S. Minimal important difference to infer changes in health-related quality of life: a systematic review. *J Clin Epidemiol.* 2017;89:188–98.
18. Sorensen SV, Peng S, Dorman E, Cote S, Tambour M, Pan F, et al. The cost-effectiveness of ibrutinib in treatment of relapsed or refractory chronic lymphocytic leukemia. *Health Econ Outcome Res.* 2016;2(4).
19. Barnes JI, Divi V, Begaye A, Wong R, Coutre S, Owens DK, et al. Cost-effectiveness of ibrutinib as first-line therapy for chronic lymphocytic leukemia in older adults without deletion 17p. *Blood Adv.* 2018;2(15):1946–56.
20. Sinha R, Redekop WK. Cost-effectiveness of ibrutinib compared with obinutuzumab with chlorambucil in untreated chronic lymphocytic leukemia patients with comorbidities in the United Kingdom. *Clin Lymphoma Myeloma Leuk.* 2018;18(2):e131–e42.

