Zanubrutinib
The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.
Rejected
Section:
8. Immunomodulators and antineoplastics 8.2. Antineoplastics and supportive medicines 8.2.2. Targeted therapies
ATC codes: L01EL03
Indication
Chronic lymphocytic leukaemia or small lymphocytic lymphoma ICD11 code: 2B52.0
INN
Zanubrutinib
Medicine type
Chemical agent
List type
Complementary
Formulations
Oral > Solid: 80 mg
EML status history
Application rejected in 2021 (TRS 1035)
Application rejected in 2023 (TRS 1049)
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
Zanubrutinib
DrugBank
Zanubrutinib
Expert Committee recommendation
☐
The Expert Committee acknowledged the role of targeted therapy with Bruton tyrosine kinase inhibitors in the treatment of CLL/SLL, especially in high-income countries, and recalled the recommendation of the 2021 Committee to include ibrutinib on the EML for patients with relapsed/refractory disease as there was compelling evidence of relevant benefit and improved tolerability compared with chemoimmunotherapy. The Committee noted the results of clinical trials comparing zanubrutinib with bendamustine–rituximab in previously untreated patients, and with ibrutinib in patients with relapsed/refractory disease, which showed promising survival gains. However, the Committee considered that the magnitude of these gains may be limited and noted that few long-term data were currently available. The Committee also noted the toxicity concerns highlighted by the Cancer Medicines Working Group and considered longer-term data would be informative to confirm the safety profile of zanubrutinib. The Committee also noted the high price of zanubrutinib and considered that at this price, it was unlikely to be cost-effective or affordable in most low- and middle-income settings. The Committee also considered that the substitution of ibrutinib with zanubrutinib would not necessarily be associated with savings in health budgets as proposed in the application, because lower ibrutinib doses than those described in the application could be used in clinical practice. The Expert Committee therefore did not recommend the addition of zanubrutinib to the complementary list of the EML for the treatment of CLL/SLL. However, recognizing the role of Burton tyrosine kinase inhibitors in the treatment of CLL/SLL, the Committee recommended that the data continue to be evaluated as the evidence evolves and matures.
Background
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An application for inclusion of the Bruton tyrosine kinase inhibitor zanubrutinib on the EML for the treatment of relapsed or refractory CLL/SLL was considered by the Expert Committee in 2021 (1). The Expert Committee noted that targeted therapy with Bruton tyrosine kinase inhibitors was emerging as the cornerstone of treatment for CLL/SLL in high-income countries, replacing chemoimmunotherapy as the accepted standard of care because these inhibitors were more effective, had less acute toxicity and had minimal risk of the development of secondary leukaemias. The 2021 Committee considered that the application for inclusion of zanubrutinib on the EML for the proposed indication was premature. The available data on efficacy and safety were limited to one phase II single-arm trial, with a small number of participants. Comparative evidence of efficacy and safety versus other treatments, for example ibrutinib, was also lacking. The available data were therefore considered insufficient to evaluate the clinical benefit and safety of zanubrutinib at that time. The 2021 Committee also noted that zanubrutinib was expensive, had unknown cost–effectiveness and had very limited global regulatory approval and availability. Therefore, the Committee did not recommend its inclusion on the EML. However, recognizing the emerging importance of Bruton tyrosine kinase inhibitors as a therapeutic class in the treatment of CLL for both first- and second-line treatment, the Committee advised that it would welcome an application including zanubrutinib and other Bruton tyrosine kinase inhibitors for inclusion on the EML in the future when mature data are available. At the same meeting, the Expert Committee recommended the addition of ibrutinib, another Bruton tyrosine kinase inhibitor, to the complementary list of the EML for treatment of relapsed/refractory CLL. The Committee considered that the data in this case were compelling for an important sustained benefit and improved tolerability for all patients with CLL (i.e. with or without 17p deletion). The

Committee acknowledged the potential of ibrutinib as a first-line treatment, particularly in the subgroup of patients 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 (1). The EML currently also includes bendamustine and rituximab as chemoimmunotherapy for CLL.

Public health relevance

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CLL/SLL is the main non-Hodgkin lymphoma (NHL) subtype occurring mainly in middle-aged and elderly people. CLL and SLL are indolent B-cell malignancies that are often considered to be different clinical presentations of one disease, the major difference being whether a patient presents with adenopathy alone (SLL) or with an elevated lymphocyte count (CLL). In many high-income countries, CLL is the most common leukaemia in adults and accounts for 5–11% of non-Hodgkin lymphoma with an annual incidence of 4.2 per 100 000 people (2). The annual incidence increases to more than 30 per 100 000 people in those aged 80 years and older. The median age at diagnosis is 72 years (3). CLL is much less prevalent in Asian countries, where it accounts for 1–3% of non-Hodgkin lymphoma and has an age-adjusted incidence of 0.2–0.3 per 100 000 people (4). During 2010–2016, the 5-year relative survival of CLL/SLL patients in the United States was 85.7% with lower survival in older age groups. The 5-year relative survival of CLL/SLL patients aged 0–19 years, 20–64 years and 65 years and older was 93.0%, 92.4% and 81.1%, respectively (5). Although mostly considered an indolent disease, clinical presentations vary widely, and CLL/SLL is still a life-limiting and incurable illness. All patients who require therapy will relapse at some point. The prognosis of patients with CLL/SLL is highly heterogeneous with median overall survival of about 10 years. Some patients can survive for many years while about 20% have a very aggressive presentation and a median overall survival of 1.5–3.0 years (6). The presence of a deletion of the short arm of chromosome 17p is associated with more rapid disease progression and poor response to treatment.

Benefits

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The SEQUOIA trial was a randomized, phase III trial comparing zanubrutinib and bendamustine–rituximab in 590 patients with previously untreated CLL/SLL (7). Patients without 17p deletion (del(17p13·1)) were randomly assigned to receive zanubrutinib (group A) or bendamustine–rituximab (group B). Patients with 17p deletion (del(17p13·1)) were enrolled in group C and received zanubrutinib. The primary endpoint was progression-free survival assessed by an independent review committee in the intention-to-treat population in groups A and B. At median follow-up of 26.2 months, median progression-free survival had not been reached in either group. The estimated rate of progression-free survival at 24 months was 85.5% (95% confidence interval (CI) 80.1% to 89.6%) in group A, compared with 69.5% (95% CI 62.4% to 75.5%) in group B (hazard ratio (HR) 0.42, 95% CI 0.28 to 0.63). The progression-free survival benefit was consistently observed across key patient subgroups. Estimated overall survival at 24 months was similar between the two arms: 94.3% (95% CI 90.4% to 96.7%) in group A and 94.6% (95% CI 90.6% to 96.9%) in group B. Median overall survival had not yet been reached in either group. In group C, with a median follow-up of 30.5 months, median progression-free survival was not reached, estimated 24-month progression-free survival was 88.9% (95% CI 81.3% to 93.6%) and estimated 24-month overall survival was 93.6% (95% CI 87.1% to 96.9%). An interim analysis of health-related quality of life outcomes was assessed using patient reported outcomes using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and EQ-5D-5L VAS (8). Patients who were treated with zanubrutinib showed greater improvements in health-related quality of life at weeks 12 and 24 compared with patients treated with bendamustine–rituximab. At 24 weeks, these differences were significantly higher for zanubrutinib in global health status, physical functioning, role functioning, and reduction in diarrhoea, fatigue and nausea/vomiting. The ALPINE study was a randomized, phase III trial comparing the efficacy and safety of zanubrutinib versus ibrutinib in patients with relapsed/refractory CLL/SLL (9). Patients were randomized 1:1 to zanubrutinib 160 mg orally twice daily or ibrutinib 420 mg orally once daily. After a median follow up of 29.6 months, zanubrutinib was superior to ibrutinib for progression-free survival among 652 patients (HR for disease progression or death, 0.65, 95% CI 0.49 to 0.86), as assessed by the investigators; the results were similar to those as assessed by an independent review committee. At 24 months, the investigator-assessed rates of progression-free survival were 78.4% in the zanubrutinib group and 65.9% in the ibrutinib group. Median progression-free survival was not reached in the zanubrutinib group and was 34.2 months (95% CI 33.3 months to not estimable) in the ibrutinib group. Among patients with a 17p deletion, a TP53 mutation or both, those who received zanubrutinib had longer progression-free survival than those who received ibrutinib (HR for disease progression or death 0.53, 95% CI 0.31 to 0.88). Progression-free survival across other major subgroups consistently favoured zanubrutinib. In the intention-to-treat population, zanubrutinib had a higher overall response rate (assessed by an independent review committee) than ibrutinib (86.2% versus 75.7%), with a rate of partial response with lymphocytosis or better of 91.7% versus 83.1%. An interim analysis of health-related quality of life outcomes was done for patient-reported outcomes using EORTC QLQ-C30 and EQ-5D-5L VAS. Compared with baseline, the positive improvements in health-related quality of life, as assessed by disease-related symptoms and treatment-related effects and functioning, were greater in cycle seven (6 months after the start of therapy), which suggests that treatment with zanubrutinib could potentially alleviate disease burden earlier than ibrutinib in this patient population. The health-related quality of life results align with results from the interim analysis of ALPINE showing that rates of adverse events such as atrial fibrillation, major bleeding and adverse events leading to discontinuation or death were lower in patients treated with zanubrutinib than ibrutinib (10). Study BGB-3111-205 was a single-arm, open-label phase II study evaluating safety and efficacy of zanubrutinib in relapsed/refractory CLL/SLL (11). After a median follow up of almost 34 months, investigator-assessed overall response rate was 87.9%, with 6.6% of patients achieving a complete response, 69.2% achieving a partial response (PR), and 12.1% achieving a PR with lymphocytosis. Overall response rate was generally consistent across all subgroups analysed, including patients with high-risk cytogenetics (12). Study BGB-3111-AU-003 was a phase I/II open-label, multiple dose, dose escalation and expansion study to investigate the safety and pharmacokinetics of zanubrutinib in 123 patients with treatment naïve or relapsed/refractory CLL/SLL (13). After a median follow-up of 47.2 months, the overall response rate was 95.9% % (treatment naïve, 100%; relapsed/refractory 95%), with 18.7% achieving complete response. Ongoing response at 3 years was reported in 85.7% of patients. The overall response rate in patients with the del(17p)/tumour protein p53 mutation was 87.5%. The 2- and 3-year estimated progression-free survival was 90% and 83%, respectively.

Harms

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In the phase III SEQUOIA study of zanubrutinib versus bendamustine–rituximab, grade 3 or higher adverse events were

reported in 126 (52.5%) and 181 (79.7%) participants in the zanubrutinib and brentuximab–rituximab arms, respectively. Serious adverse events were reported in 88 (36.7%) and 113 (49.8%) participants, respectively. The most frequently reported adverse events ≥ grade 3 in the zanubrutinib arm were infections (16.3%), neutropenia (11.7%), other cancers (7.1%), hypertension (6.3%) and bleeding and major bleeding (both 3.8%). The most frequently reported adverse events ≥ grade 3 in the brentuximab–rituximab arm were neutropenia (51.1%), infections (18.9%), thrombocytopenia (7.9%) and hypertension (4.8%) (7). In the phase III ALPINE study of zanubrutinib versus ibrutinib, treatment discontinuation was lower with zanubrutinib (26.3%) versus ibrutinib (41.2%), with most discontinuations due to adverse events (16.2% versus 22.8%) or progressive disease (7.3% versus 12.9%). Discontinuation due to cardiac disorders occurred in 0.3% versus 4.3% of participants. Rates of ≥ grade 3 adverse events, serious adverse events, dose interruptions and dose reductions were also lower with zanubrutinib compared with ibrutinib. The proportion of participants with new-onset atrial fibrillation/flutter was lower with zanubrutinib than ibrutinib (5.2% versus 13.3%); rates of other adverse events of special interest were similar between treatments. No grade 5 adverse events due to cardiac disorders occurred with zanubrutinib, whereas these occurred in six (1.9%) participants treated with ibrutinib (9). The ASPEN trial was a pivotal, randomized, open-label, phase III, study comparing zanubrutinib with ibrutinib in patients with Waldenström macroglobulinaemia (14). In the long-term follow up of ASPEN, zanubrutinib was associated with fewer adverse events leading to death, treatment discontinuation, and dose reduction compared with ibrutinib. The prevalence of atrial fibrillation, hypertension and bleeding were lower in the zanubrutinib arm at all time intervals (15). Safety data from the phase II BGB-3111-205 study (11) were the same as those reported in the 2021 application (1). In the phase I/II BGB-3111-AU-003 study, 76 (61.8%) participants experienced at least one grade 3 or higher adverse event. Five (4.1%) participants discontinued zanubrutinib therapy due to an adverse event; three were deemed unrelated and two related to zanubrutinib therapy. One person experienced an adverse event leading to death, which was deemed unrelated by investigators (13).

Cost / cost effectiveness

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Comparative cost–effectiveness studies for zanubrutinib in the treatment of CLL/SLL are lacking. The application presented a comparison of the costs per day of zanubrutinib (all indications) and ibrutinib (two groups of indications: CLL/SLL/Waldenström macroglobulinaemia and mantle cell lymphoma/marginal zone lymphoma) in 19 upper middle- and high-income countries. The average price difference for zanubrutinib compared with ibrutinib was –0.3% for CLL/SLL/Waldenström macroglobulinaemia indications and –24.1% for mantle cell lymphoma/marginal zone lymphoma indications. The application asserted that substitution of ibrutinib with zanubrutinib would be associated with health budget savings, based on the assumption that zanubrutinib had clinical advantages and a cheaper price than ibrutinib.

WHO guidelines

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WHO guidelines for treatment of CLL/SLL are not currently available.

Availability

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As of 30 November 2022, zanubrutinib was approved for selected indications (other than CLL/SLL) in 61 markets including Australia, Canada, China, European Union, Republic of Korea, Switzerland, the United Kingdom, and the United States. Additional regulatory submissions are under review around the world. Zanubrutinib is currently approved for use in the treatment of CLL/SLL only in China (relapsed/refractory disease only) and the European Union. Regulatory approval in other jurisdictions is ongoing.

Other considerations

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The technical team in cancer in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical department commented that there was insufficient mature overall survival data currently available to justify inclusion of zanubrutinib on the Model List. In addition, the technical department noted the need for additional data about toxicity and feasibility of use in settings with weaker health systems without specialized clinical services. The EML Cancer Medicines Working Group reviewed the application and advised that did not support the inclusion of zanubrutinib on the EML for the treatment of CLL/SLL at this time. The working Group noted that while data supported progression-free survival gains with zanubrutinib compared to ibrutinib, it considered that the magnitude of these gains might be limited. The Working Group also noted that few long-term and real-world data were available. Furthermore, the Group acknowledged the following limitations for zanubrutinib: high rates of toxicity (particularly neutropenia); remaining uncertainty on a better safety profile compared with ibrutinib for bleeding, hypertension and atrial fibrillation; and limited information on prices with uncertain cost–effectiveness (given that lower doses can be used with ibrutinib compared with those proposed in the application).

☐ Show references Hide references

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