

## CADTH Reimbursement Recommendation

# Zanubrutinib (Brukinsa)

**Indication:** For the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy

**Sponsor:** BeiGene Canada ULC

**Final recommendation:** Do not reimburse

**ISSN:** 2563-6596

**Disclaimer:** The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third-party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

The copyright and other intellectual property rights in this document are owned by CADTH and its licensors. These rights are protected by the Canadian *Copyright Act* and other national and international laws and agreements. Users are permitted to make copies of this document for non-commercial purposes only, provided it is not modified when reproduced and appropriate credit is given to CADTH and its licensors.

**Redactions:** Confidential information in this document may be redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines*.

**About CADTH:** CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

**Funding:** CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

## What Is the CADTH Reimbursement Recommendation for Brukinsa?

CADTH recommends that Brukinsa (zanubrutinib) should not be reimbursed by public drug plans for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy.

## Why Did CADTH Make This Recommendation?

- While evidence from 2 clinical trials showed a response in patients treated with Brukinsa, there is uncertainty in how well patients respond to Brukinsa and how Brukinsa compares to other treatment for MCL.
- There was no evidence demonstrating improvement in quality of life, since there was no quality of life evidence collected in either clinical trial.
- It is unclear whether Brukinsa meets the following needs identified by patients: faster remission and longer life, disease and symptom control, better quality of life, and fewer side effects.

## Additional Information

### What is MCL?

MCL is an aggressive subtype of B-cell non-Hodgkin lymphoma that affects the lymphatic system. In Canada, there are approximately 500 to 600 new cases of MCL diagnosed each year. MCL occurs more frequently in men and is usually diagnosed in patients who are 60 to 70 years old.

### Unmet Needs in MCL

Effective treatment that allows patients to live longer and have better quality of life is needed.

### How Much Does Brukinsa Cost?

Treatment with Brukinsa is expected to cost approximately \$99,256 per patient per year.

## Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that zanubrutinib not be reimbursed for the treatment of adult patients with MCL who have received at least 1 prior therapy.

## Rationale for the Recommendation

Two single-arm multi-centre studies were included in this review: Study 206 evaluated the efficacy of zanubrutinib in patients with relapsed/refractory (R/R) MCL, and Study 003 assessed the safety and tolerability of zanubrutinib in patients with B-cell lymphoid malignancies. Although patients exhibited an objective response in both studies, there was a high degree of uncertainty regarding the magnitude of clinical benefit directly attributed to zanubrutinib, due to the limitations associated with the open-label, single-arm study design; lack of control group; and lack of statistical testing in other important outcomes such as overall survival and progression-free survival. Due to the absence of a comparator arm, the potential clinical benefit of zanubrutinib compared to other currently available treatment options is unknown. Quality of life was not assessed in either study. The sponsor submitted a matched-adjusted indirect comparison (MAIC) comparing zanubrutinib to ibrutinib in patients with R/R MCL. However, the analytical approach resulted in a low effective sample size, making the estimates of comparative efficacy subject to substantial uncertainty. Ultimately, pERC concluded that there is uncertainty in the clinical benefit and harms of zanubrutinib compared to other relevant treatment options based on the evidence provided by these trials.

Patients expressed a need for faster remission and longer survival; disease and symptom control; quality of life improvement; fewer side effects; as well as ease and simplicity of, and access to, treatment administration. Given the totality of evidence, pERC concluded that zanubrutinib met 1 important need identified by patients, in terms of ease and simplicity of treatment administration as an oral therapy.

## Discussion Points

- pERC discussed that both Study 206 and Study 003 were single-arm studies that did not have a control group. pERC recognized that the response rate with zanubrutinib may appear similar to ibrutinib and is possibly associated with less toxicity (e.g., atrial fibrillation). However, the lack of direct comparison and limitations of the sponsor's submitted indirect treatment comparison (ITC) precluded pERC's ability to draw any robust conclusions regarding the potential efficacy or safety benefit. Ultimately, pERC concluded that there is uncertainty in the clinical benefit and harms of zanubrutinib compared to other relevant treatment options resulting from 2 small single-arm studies with no control group and an ITC that cannot be interpreted as a comparison due to the small effective sample size and the statistical methods used.
- pERC noted the differences in response rates between Study 206 and Study 003 and acknowledged that differences in the population of trials (e.g., younger patients in Study 206 and different geographic locations) may have accounted for the differences in

response rates observed between the 2 trials. This observed difference in overall response rate (ORR) contributed to the uncertainty in the evidence.

- pERC acknowledged zanubrutinib is a potential treatment alternative for patients at risk of specific toxicities from other Bruton tyrosine kinase (BTK) inhibitors, or for patients who are intolerant of other BTK inhibitors. pERC discussed that these patients would benefit from the availability of an alternative BTK inhibitor with a different toxicity profile. pERC discussed that zanubrutinib has the potential to fulfill a need for patients who have contraindications or who develop intolerance to ibrutinib; however, pERC felt that the current available evidence limited their ability to evaluate the clinical benefit and harms of zanubrutinib in this specific population, and highlighted that robust disease-specific clinical trial data, quality of life data, and pharmacoeconomic analysis in this specific population are needed.
- While pERC acknowledged the rarity of MCL, pERC discussed the feasibility of conducting a randomized controlled trial (RCT) in this setting with zanubrutinib, given that a phase III RCT was previously performed in R/R MCL. pERC discussed that at the time ibrutinib was approved for MCL with temsirolimus as the comparator in the pivotal trial, there was no standard of care for R/R MCL in Canada; however, pERC highlighted that ibrutinib is now the standard of care. pERC acknowledged the input from clinical experts and clinician and patient groups, and deliberated on the new data provided by the sponsor (e.g., non-MCL specific safety data, phase II and real-world evidence data, and Pharmaceutical Benefits Advisory Committee-submitted MAIC). No new data provided have altered pERC conclusions, as pERC felt that robust disease-specific data (e.g., real-world evidence in a Canadian setting) and quality of life data are needed. Direct comparative evidence would address the uncertainty in clinical benefit and the harms of zanubrutinib for the treatment of adult patients with MCL who have received at least 1 prior therapy.

## Background

MCL is an aggressive B-cell lymphoma, arising from cells in the mantle zone of the lymph node. It is a relatively rare cancer, and accounts for 5% to 10% of all cases of non-Hodgkin Lymphoma (NHL). The Canadian Cancer Society estimated 11,100 Canadians would be diagnosed with NHL in 2021. MCL can begin with an indolent phase, and a small percentage of patients will remain in this indolent phase. In most patients, MCL can become aggressive; it is often diagnosed at a late stage, and often presents in the gastrointestinal tract, bone marrow, blood, and other non-lymph node sites. The median survival of patients with MCL is between 4 and 5 years. Definitive diagnosis of MCL is achieved through biopsy, which is also used to distinguish it from other NHL subtypes. Imaging is often used to determine the areas of involvement, using CT or PET scans.

Approximately 10% to 15% of patients with MCL do not require treatment, at least initially, and are instead managed with watchful waiting. Most patients with MCL require immediate treatment, and the first decision clinicians face is whether patients are eligible for an autologous stem cell transplant (ASCT). Those eligible for ASCT undergo intensive multi-drug chemotherapy regimens followed by a stem cell transplant. Rituximab maintenance is used post-ASCT for 3 years. Those who are transplant-ineligible (medically unfit or, in most centres, > 65 years of age) receive bendamustine plus rituximab, followed by rituximab maintenance

until progressive disease (PD) or for 2 years, whichever occurs sooner. At relapse, most patients would receive a BTK inhibitor, namely ibrutinib. In patients who had a very long remission to initial therapy and wished to avoid indefinite BTK inhibitor therapy, other options that would be considered include bortezomib combination regimens. Therapy for R/R MCL is considered palliative, with the goal of improving quality and quantity of remaining life.

Zanubrutinib has been approved by Health Canada for the treatment of adult patients with MCL who have received at least 1 prior therapy. Zanubrutinib is a BTK inhibitor. It is available as 80 mg oral capsules and administered at a dose of 320 mg orally once daily or 160 mg orally twice daily. Zanubrutinib is also indicated for the treatment of adults with Waldenström macroglobulinemia and was reviewed by CADTH for this indication. The sponsor's reimbursement request for zanubrutinib is for adult patients with MCL who have received at least 1 prior therapy, which is the same as the Health Canada-approved indication.

## Sources of Information Used by the Committee

To make their recommendation, the committee considered the following information:

- a review of the 2 single-arm multi-centre clinical studies in adult patients with R/R MCL
- patients' perspectives gathered by 1 patient group, Lymphoma Canada
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with MCL who have received at least 1 prior therapy
- input from 2 clinician groups, including Lymphoma Canada and the Ontario Health – Cancer Care Ontario Drug Assessment Committee (OH-CCO DAC)
- a review of the pharmacoeconomic model and report, and MAIC submitted by the sponsor
- feedback on initial recommendation from stakeholders and new data provided by the sponsor.

## Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from clinical experts consulted by CADTH for the purpose of this review.

### Patient Input

Lymphoma Canada submitted patient input for this review, based on 2 online surveys of patients with MCL conducted between October 19, 2020, and January 11, 2021, and between September 20, 2021, and October 20, 2021, for a total of 85 respondents.

Respondents reported MCL symptoms such as fatigue, and symptoms caused by low red blood cell counts that affected their ability to travel, work, exercise, and complete household chores, causing detrimental effects on their quality of life. According to respondents, the most

difficult MCL treatment side effects included fatigue, nausea or vomiting, neurocognitive effects such as brain fog or headaches, and hair loss.

Respondents reported that they expect the following key outcomes from any new drug or treatment: faster remission, delay in disease progression, control of disease and symptoms, improved quality of life, and fewer side effects. Most respondents indicated a desire to have a choice in their treatment selection and most would prefer a pill option rather than an IV treatment.

## Clinician Input

### Input From Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH on this review noted that treatments for relapsed MCL had not been very effective at generating prolonged remission, until the emergence of the BTK inhibitors. The currently funded BTK inhibitor improved many of the treatment goals, however there are side effects in some patients.

The clinical experts believe that zanubrutinib would be an alternative in patients who are unable to tolerate ibrutinib or 1 of its alternatives. Patients with R/R MCL who have not progressed on another BTK inhibitor would be candidates for zanubrutinib. The clinical experts believed that zanubrutinib may carry a marginally higher risk of neutropenia than ibrutinib, and therefore patients who are having issues with neutropenia may not be good candidates for a switch.

The clinical experts believe that the most effective methods for assessing response to treatment are clinical and radiological assessments of lymph node size, and response to therapy would be indicated by a reduction in lymph node size, although preventing progression of lymphadenopathy and/or disease symptoms would also be considered valuable. Response to treatment would likely be assessed monthly early on, then perhaps every 3 months, and treatment should be discontinued when there is clinical or radiological evidence of disease progression or intolerable side effects.

### Clinician Group Input

Experts assembled by Lymphoma Canada, as well as the OH-CCO DAC, provided input.

There were no major discrepancies between input provided by the clinical experts consulted by CADTH on this review and the clinician groups.

### Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for zanubrutinib:

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues

- potential need for a provisional funding algorithm.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

## Clinical Evidence

### Pivotal Studies and Protocol-Selected Studies

#### Description of Studies

Two single-arm multi-centre sponsor-funded trials, Study 206 (N = 86) and Study 003 (N = 32), were included in this review. The objective of Study 206 was to evaluate the efficacy of zanubrutinib in patients with R/R MCL as measured by ORR and assessed by an independent review committee using the Lugano criteria. This single-arm study was conducted entirely in China and enrolled 86 patients after an initial screening phase of up to 28 days, followed by a single-arm treatment phase where patients received zanubrutinib 320 mg daily orally, and a follow-up phase. The treatment phase could last up to 3 years, until PD, unacceptable toxicity, death, withdrawal of consent, or until it was terminated by the sponsor for the final analysis. The primary outcome was ORR, while secondary outcomes included progression-free survival (PFS) and duration of response (DOR), while overall survival (OS) was an exploratory outcome. The data cut-off for the final clinical study report (CSR) was September 8, 2020. Study 003 was divided into 2 parts. The primary objectives of Part 1 were to determine the safety and tolerability of zanubrutinib in patients with B-cell lymphoid malignancies, and to determine the recommended phase II dose regimen for oral zanubrutinib. The primary objective of Part 2 was to further assess the safety and tolerability of zanubrutinib administered orally either once or twice daily. There were sites in North America, Europe, Australia, New Zealand, and South Korea, although no specific Canadian sites were identified. The total daily dose of zanubrutinib was 320 mg, administered either as a single daily dose or split twice daily. Study 003 was not designed to assess efficacy outcomes, but did report outcomes such as ORR, PFS and OS. The data cut-off for the CSR was March 31, 2021.

Patients had a median age of 60.5 years in Study 206 and 70.5 years in Study 003. The majority of patients were male in both Study 206 (78%) and Study 003 (69%). In Study 206, all patients were Asian, while in Study 003 the majority of patients were White (78%). The majority of patients (70%) in Study 206 had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, while in Study 003 there were a similar number of patients with an ECOG status of 0 (47%) or 1 (44%), and the majority of patients in Study 206 (74%) and Study 003 (88%) had stage IV disease. The majority of patients (71%) in Study 206 had 2 or more prior therapies, while the majority of patients in Study 003 had only 1 prior therapy.

#### Efficacy Results

In Study 206, by the time of the final CSR, with a median follow-up of 36.8 months (range = 0.3 to 41.6), the median OS was still not estimable. At 30 months, 77.6% of patients were alive (95% CI, 66.8 to 85.3) and at 36 months, 74.8% of patients were alive (95% CI, 63.7 to 83.0). In Study 003, with a median follow-up of 45.8 months (95% CI, 42.0 to 48.6) at the final analysis, the median OS was also not estimable.

In Study 206, in the final analysis, after a median follow-up of 33.3 months (range = 0.0 to 38.9 months), the median PFS was 33.0 months (95% CI, 19.4 to not estimable). In Study 003, in the final analysis after a median follow-up time for PFS of 40.0 months (95% CI, 28.3 to 45.1), the median PFS was 21.1 months (95% CI, 13.2 to not estimable).

In Study 206, the ORR was 83.7% (95% CI, 74.2 to 90.8), which ruled out the pre-specified null hypothesis of 40% with a 1-sided P value of less than 0.0001. The complete response (CR) rate was 77.9% (95% CI, 67.7 to 86.1). In Study 003, the ORR at the final analysis was 90.6% (95% CI, 75.0 to 98.0) and the CR rate was 31.3% (95% CI, 16.1 to 50.0). No statistical analysis was planned.

In Study 206, the median DOR in the 72 patients who achieved an ORR was 24.9 months (95% CI, 23.1 months to not reached). The sponsor noted that because the median was reached with the last event occurring while only 3 patients were at risk, the median DOR estimate was "unstable." In Study 003, the median DOR at the final analysis was 25.2 months, after a median follow-up of 36.9 months (95% CI, 32.3 to 42.3).

Health-related quality of life was not assessed in the included studies.

## Harms Results

Adverse events (AEs) were reported in 97% of patients in both studies; 50% of patients in Study 206 reported a grade 3 or higher AE, and 69% of patients in Study 003 also reported a grade 3 or higher AE. The most common AEs in Study 206 were decreased neutrophil count (47% of patients) and upper respiratory tract infections (38%), and the most common grade 3 or higher AEs were decreased neutrophil count (19%) and lung infection (9%). The most common AEs in Study 003 were diarrhea (47%), constipation (41%), and rash (34% of patients), and the most common grade 3 or higher AEs were anemia (12.5%) and pneumonia (12.5%).

Serious adverse events (SAEs) occurred in 29% of patients in Study 206 and in 59% of patients in Study 003, with the most common SAE being pneumonia (12% in Study 206; 12.5% in Study 003).

In Study 206, 9% of patients had at least 1 AE leading to discontinuation of the study drug, and pneumonia was the most common event, occurring in 2% of patients. In Study 003, 28% of patients had at least 1 AE leading to discontinuation of the study drug, and in 6% of patients this was pneumonia.

In Study 206, 24% of patients died, 9% within 30 days of their last dose of the study drug and 15% more than 30 days after their last dose of the study drug. Among the patients who died within 30 days of their last dose, most (7% overall) died due to an AE, while the remaining deaths were due to PD. For those deaths that occurred more than 30 days after their last dose of the study drug, most (12% overall) were due to PD, while the remaining 3 deaths were due to AEs and "other" causes. In Study 003, 38% of patients died, 16% within 30 days of their last dose of the study drug (9% due to an AE), and 22% died more than 30 days after their last dose of the study drug (16% due to PD).

Notable harms in Study 206 included infections (65% of patients; 19% grade  $\geq 3$ ), decreased platelet count (33%; 7% grade  $\geq 3$ ), hemorrhage (36%; 1% grade  $\geq 3$ ), and anemia (17%; 6% grade  $\geq 3$ ). In Study 003, hemorrhage occurred in 62.5% of patients and infections occurred in 72% of patients.

## Critical Appraisal

Both of the included studies lacked a control group. This limits interpretation of both efficacy and harms, as there is no control group available as a basis for comparison, and because all patients are aware of the treatments they are receiving. The outcomes most at risk of bias from patient unblinding are typically patient-reported outcomes such as health-related quality of life; however, this outcome was not assessed in the included studies.

ORR was the only outcome that was formally assessed using a statistical comparison, and this was only in Study 206. For this analysis, the sponsor used a historical control of 40% as a reference. Data for key clinical outcomes like OS and PFS were reported; however, the lack of statistical comparisons and the lack of a control group makes it challenging to interpret this data. Median OS was not estimable and there is uncertainty around those outcomes that were estimable, due to the lack of comparison. Study 003 was a phase I/II study and was not designed to evaluate efficacy, since only toxicities were important in the dose-finding and initial phase II outcomes.

## Indirect Comparisons

### Description of Studies

No indirect comparisons of zanubrutinib were found in the peer-reviewed literature. A MAIC was provided by the sponsor, comparing zanubrutinib to ibrutinib in patients with R/R MCL. Data to inform this analysis was taken from Study 206 and Study 003, both of which were available at the individual patient level and were matched to a pooled analysis population from 3 ibrutinib trials (PCYC-1104-CA, RAY, and SPARK) using entropy weighting adjustment. The ITC evaluated differences in OS, PFS, response, and safety between the weighted zanubrutinib population relative to the pooled ibrutinib population.

### Efficacy Results

Following entropy weighting adjustment, the zanubrutinib analysis population was reduced to an effective sample size (ESS) of 37, from an available total population of 117. ORR rate did not demonstrate statistically significant differences between the weighted zanubrutinib (ORR: 77.7%; 95% CI, 63 to 92.4) and ibrutinib (ORR: 65.7%; 95% CI, 60.6 to 70.5) treatment groups. Similarly, CR rate did not demonstrate statistically significant differences between weighted zanubrutinib (CR: 25.5%; 95% CI, 12.5 to 38.5) and ibrutinib (CR: 20%; 95% CI, 16 to 24.4) treatment groups. PFS did not demonstrate statistically significant differences between the weighted zanubrutinib (restricted mean progression-free survival time [RMST]: 13.9 months) and ibrutinib (RMST: 12.6 months) treatment arms (hazard ratio [HR] of zanubrutinib versus ibrutinib = 0.92; 95% CI, 0.63 to 1.33). Similarly, OS did not demonstrate statistically significant differences between the weighted zanubrutinib (RMST: 21.2) and ibrutinib (RMST: 18.4) treatment arms (HR of zanubrutinib versus ibrutinib = 0.74; 95% CI, 0.43 to 1.26).

### Harms Results

No formal statistical comparison was made on the differences in safety events between the 2 analysis populations, and was limited to a description of hematologic toxicities.

## Critical Appraisal

The analytical approach used resulted in a low ESS, making estimates of comparative efficacy subject to uncertainty. The low ESS is indicative of large differences between the unadjusted patient populations, which demonstrated large between-population differences

pre-adjustment. Post-adjustment balance of patient characteristics was assessed using an approach that still allowed for differences between patient populations, and therefore residual confounding due to specified and unspecified patient characteristics may influence the results presented. No conclusions can be made with regard to the ITC, owing to the statistical approaches used alongside the large differences in patient populations of the trials within the comparison.

No formal comparisons of patients' safety or patients' quality of life were made, meaning that comparisons to ibrutinib are not possible from the evidence presented.

### Other Relevant Evidence

There was no other relevant evidence available for this review.

## Economic Evidence

### Cost and Cost-Effectiveness

**Table 1: Summary of Economic Information**

Component	Description
Type of economic evaluation	Cost-minimization analysis
Target population	Adult patients with MCL who have received at least one prior therapy
Treatment	Zanubrutinib, 320 mg once daily or 160 mg twice daily
Submitted price	Zanubrutinib: \$67.98 per 80 mg capsule
Treatment cost	The annual cost of zanubrutinib is \$99,256 per patient.
Comparator	Ibrutinib
Perspective	Canadian publicly funded health care payer
Time horizon	One year
Key data source	Sponsor-submitted ITC of zanubrutinib compared to ibrutinib based on Study 003 and Study 206 (zanubrutinib) and PCYC-1104, SPARK, and RAY trials (ibrutinib). The studies for each treatment were pooled for the analysis, and individual patient data for the zanubrutinib studies were matched to the pooled ibrutinib cohort based on sponsor-defined criteria.
Costs considered	Drug acquisition costs
Submitted results	Zanubrutinib is associated with an incremental cost savings of \$46,503 per patient annually.
Key limitations	<ul style="list-style-type: none"> <li>• In the absence of a head-to-head comparison between zanubrutinib and ibrutinib, a sponsor-commissioned ITC was submitted, which did not provide strong clinical evidence on comparable clinical efficacy between zanubrutinib and ibrutinib due to significant methodological issues with the approach taken. As such, the comparative clinical efficacy of zanubrutinib and ibrutinib, which was used to support the cost-minimization analysis, could not be validated.</li> <li>• The sponsor's analysis considers ibrutinib to be the only relevant comparator for zanubrutinib, that there will be no difference in costs due to duration of treatment, and that no treatment switching will</li> </ul>

Component	Description
	<p>occur. Feedback from the clinical experts consulted by CADTH indicated that there may be patients who switch from ibrutinib to zanubrutinib due to toxicity or adverse events experienced on ibrutinib, as long as they responded to ibrutinib. This would extend the duration of treatment on a BTK inhibitor instead of a patient moving to an alternate treatment regimen.</p> <ul style="list-style-type: none"> <li>• The sponsor's 1-year time horizon may not accurately capture all relevant costs, as treatment duration with a BTK inhibitor (e.g., ibrutinib) is typically longer than one year. Duration of treatment may also be impacted by treatment switching, as noted in the previous limitation.</li> </ul>
<p><b>CADTH reanalysis results</b></p>	<ul style="list-style-type: none"> <li>• CADTH did not undertake any re-analyses comparing the drug costs of zanubrutinib and ibrutinib, due to the lack of evidence to conclude that these treatments have similar clinical efficacy. Further, zanubrutinib may extend the treatment duration with a BTK inhibitor for patients who switch from ibrutinib to zanubrutinib. This would increase costs, although the effectiveness of zanubrutinib in this setting is unknown.</li> <li>• If zanubrutinib is considered to be similar to ibrutinib in safety and efficacy, then zanubrutinib may be associated with cost savings based on its submitted price relative to the published price of ibrutinib. However, the magnitude of cost savings will be impacted by the amount of treatment switching and the negotiated price of ibrutinib.</li> </ul>

## Budget Impact

CADTH identified the following limitations with the sponsor's submission: uncertainty in estimated population size, uncertainty in the market share of zanubrutinib, exclusion of potentially relevant comparators, and assumptions regarding treatment switching.

CADTH did not conduct a base-case analysis, as the issues related to uncertainty in market share and treatment switch could not be adequately addressed with the available information in the confines of the submitted budget impact analysis (BIA). CADTH presented a series of scenario analyses to test the impact of alternative assumptions on the estimated population size and budget impact. The sponsor's base case suggested a 3-year budgetary savings of \$13,964,025. The magnitude of cost savings varied depending on the proportion of MCL patients who become refractory or relapse, as well as the proportion of R/R MCL patients treated with a BTK inhibitor, highlighting the impact of decreasing the estimated population size. However, the presence of confidential prices paid by jurisdictions is likely to reduce or eliminate these savings, depending on the discounts in place.

## pERC Information

### Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung, Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

**Initial meeting date:** March 9, 2022

**Regrets:** None

**Reconsideration meeting date:** July 12, 2022

**Regrets:** One expert committee member did not attend

**Conflicts of interest:** None