NCPE Assessment

Technical Summary

Zanubrutinib (Brukinsa®)

HTA ID: 23072

3rd September 2025

Applicant: BeiGene Ireland Limited

For adult patients with relapsed/refractory marginal zone lymphoma who have received at least one prior anti-CD20-based therapy.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of zanubrutinib (Brukinsa®).

Following assessment of the Applicant's submission, the NCPE recommends that zanubrutinib (Brukinsa®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments.*

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (BeiGene Ireland Limited) Health Technology Assessment of zanubrutinib (Brukinsa®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health-related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In August 2024, BeiGene Ireland Limited submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of zanubrutinib (Brukinsa®) for the treatment of adult patients with relapsed/refractory (R/R) marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy. BeiGene Ireland Limited is seeking reimbursement of zanubrutinib on the High-Tech Drug Arrangements.

Zanubrutinib is an inhibitor of Bruton's Tyrosine Kinase (BTK), which forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK activity. Zanubrutinib is taken orally, with a recommended total daily dose of 320mg. This can be taken as 320mg (four 80mg capsules) once daily or as 160mg (two 80mg capsules) twice daily. Treatment with zanubrutinib should be continued until disease progression or unacceptable toxicity.

It is expected that zanubrutinib will be used in the second-line setting for patients with R/R MZL who have received at least one prior anti-CD20-based therapy. This is in line with the licensed indication and clinical opinion obtained by the Review Group. The Applicant identified the Haematological Malignancy Research Network (HMRN) registry (which comprises all patients diagnosed with a haematological malignancy or related precursor conditions across 14 hospitals in the UK), supported by clinical opinion, as an appropriate source to identify comparator regimens. Here, the most common regimens received by patients with MZL in the second-line setting were chosen as comparator regimens. The Applicant referred to this as the "HMRN standard-of-care (SOC) basket" (with a sample size of n=90). This contained rituximab-based chemotherapy regimens and non-rituximab-based chemotherapy regimens, with the distribution informed by the proportion of patients receiving these regimens in the HMRN registry.

Clinical opinion, to the Review Group, indicated that there is no universal SOC for patients with R/R MZL in Ireland. However, rituximab-based therapies are widely used for patients with R/R MZL in Irish clinical practice. Thus, in the NCPE-adjusted base case, the Review

Group considered only rituximab-based chemotherapies in the HMRN SOC basket (with a sample size of n=73) to be the relevant comparator to zanubrutinib.

1. Comparative effectiveness of zanubrutinib

The clinical trial programme, to support the regulatory approval of zanubrutinib in patients with R/R MZL, was composed of the MAGNOLIA and AU-003 trials. Both were multicentre, single-arm trials. MAGNOLIA was a phase II clinical trial in participants with R/R MZL (n=68). AU-003 was a phase I/II clinical trial in participants B-cell lymphoid malignancies, including R/R MZL (n=20; data presented for this cohort only).

The MAGNOLIA trial consisted of an initial screening phase (up to 35 days), a single-arm treatment phase, and a follow-up phase until the end of the trial. Participants (n=68) received zanubrutinib at a dose of 160mg twice daily, with treatment continued until disease progression, unacceptable toxicity, death, withdrawal of consent, or study termination. The primary endpoint was overall response rate (ORR) assessed by independent review committee (IRC). The key secondary endpoints included progression-free survival (PFS) assessed by IRC and overall survival (OS). A strategy for controlling type 1 error due to multiple endpoints was not implemented; therefore, the secondary endpoints were considered exploratory only.

The AU-003 trial was composed of an initial dose escalation phase (Part 1), followed by an expansion phase (Part 2). It is the 20 participants with R/R MZL in Part 2 of the trial that are of relevance to this assessment. These data are presented here. Zanubrutinib was administered at a dose of 320mg once daily or 160mg twice daily until disease progression, unacceptable toxicity, death, withdrawal of consent, or study termination. The primary and key secondary endpoints were aligned with those of the MAGNOLIA trial. However, no null hypothesis was specified for the trial; thus, the results of primary and secondary endpoints were considered descriptive only.

At final analysis, the median duration of follow-up was 28.0 months (range: 1.6 to 32.9 months) in the MAGNOLIA trial and 39.24 months (range: 8.3 to 62.2 months) in the AU-003 trial. ORR assessed by IRC was 68.2% (95% CI 55.6 to 79.1) in the MAGNOLIA trial. Median OS

and IRC-assessed PFS were not reached at the final analysis. In the AU-003 trial, ORR assessed by IRC was 80%, (95% CI 56.3 to 94.3). Median OS and IRC-assessed PFS were not reached at the final analysis.

Given the single-arm nature of both MAGNOLIA and AU-003 trials, causal treatment effects of zanubrutinib cannot be isolated for time-to-event endpoints such as OS and PFS, nor for health-related quality of life. The Applicant did not provide evidence to support the use of ORR as a surrogate for OS and PFS. Thus, it cannot be concluded that the treatment effect observed with ORR will translate to OS or PFS benefit. This is a major limitation of the clinical evidence. Additionally, the immaturity of the trial data resulted in considerable uncertainty surrounding the PFS and OS extrapolations used in the cost-effectiveness model (CEM).

Indirect treatment comparison

Direct comparative trials of zanubrutinib versus the comparators of relevance to the decision problem were not conducted. Therefore, unanchored matching-adjusted indirect comparisons (MAICs) were used to estimate the relative effectiveness of zanubrutinib versus the HMRN SOC basket (as informed by the HMRN registry). Individual patient-level data (IPD) for the 88 participants with R/R MZL across the MAGNOLIA and AU-003 trials were pooled to inform efficacy of zanubrutinib. The unanchored MAICs reweighted IPD from pooled MAGNOLIA and AU-003 data using propensity scores, in order to align with the comparator HMRN SOC basket population (based on published aggregate summary data), in terms of a set of prognostic and effect-modifying variables. The results of these indirect treatment comparisons (ITCs) indicated that zanubrutinib was associated with an improvement in OS and PFS compared with the HMRN SOC basket in both the Applicant (n=90) and NCPE-adjusted base case (n=73).

A key limitation of the comparative effectiveness analysis was the absence of randomised comparative data and the corresponding use of unanchored ITCs, which are associated with a higher risk of bias and corresponding lower certainty of evidence than randomised controlled trials. Additionally, several key prognostic variables were not adjusted for. Therefore, there was a high risk of bias in the effect estimates, the magnitude and direction of which could not be ascertained. Results should therefore be interpreted with caution.

2. Safety of zanubrutinib

Safety data were provided for the 88 participants with R/R MZL across the MAGNOLIA and AU-003 trials. The most common treatment-emergent adverse events (TEAEs) reported in these 88 participants were diarrhoea (25%), contusion (23.9%), upper respiratory tract infection and pyrexia (15.9% each), constipation (14.8%), and nausea (12.5%). Grade three or higher TEAEs occurred in 43.2% of participants in the pooled MAGNOLIA and AU-003 trial data, the most common of which were neutropenia (9.1%), anaemia (5.7%), pyrexia (4.5%), thrombocytopaenia (3.4%), pneumonia (3.4%), COVID-19 pneumonia (3.4%), neutrophil count decreased (3.4%), diarrhoea (3.4%), and hypertension (2.3%). The safety data for zanubrutinib were generally consistent across other clinical studies and study populations. No new safety signals were identified in the MAGNOLIA and AU-003 trials. Due to the lack of a comparator arm in the MAGNOLIA and AU-003 trials, there is no direct comparative safety data available.

3. Cost effectiveness of zanubrutinib

Methods

A three-state partitioned survival model was submitted by the Applicant, comprising three mutually exclusive health states: progression-free, progressed disease, and death. The treatment effects captured by the model were the delay of disease progression and death. The proportion of patients in each health state over time were derived directly from the OS and PFS area under the curve using treatment group-specific parametric distributions fitted to time-to-event data from the MAGNOLIA and AU-003 trials, and the HMRN registry data. The MAGNOLIA and AU-003 trial data were adjusted, using the unanchored MAIC, to align with the comparator HMRN SOC basket population. In each cycle, patients accrued quality adjusted life years (QALYs) and incurred costs based on the health state occupied, treatment arm and time to treatment discontinuation (TTD).

In the absence of long-term data, the PFS and OS extrapolations of the zanubrutinib and HMRN SOC basket arms were highly uncertain. Additionally, the extrapolations of the HMRN SOC basket were considered to be potentially underestimated, based on clinical opinion.

Utility data for the progression-free health state were derived from the MAGNOLIA trial.

However, the derived progression-free utility value lacked face validity, as it was higher than that of the age-sex matched general population. Therefore, progression-free utility was capped at age-sex matched general population utility. The Review Group deemed that this approach resulted in a utility value that was highly optimistic. The progressed disease health state utility was obtained from the literature. The Review Group considered this value to be highly uncertain, due to concerns regarding the generalisability from the population from which it was derived and the method of derivation. More appropriate data sources were not identified by the Review Group. The lack of methodologically robust utility data in a relevant patient population is a key limitation. Disutilities associated with grade ≥ 3 adverse events (AEs) were included in the model.

The model also included costs related to drug acquisition, intravenous drug administration, subsequent treatment and treatments of AEs. These were generally considered to be appropriate by the Review Group.

The Review Group identified a number of key limitations in the Applicant base case, some of which were addressed in the NCPE-adjusted base case. As highlighted, in the NCPE-adjusted base case, the HMRN SOC basket (n=73) excluded non-rituximab-based chemotherapy regimens. Changes regarding other key uncertain parameters (i.e., survival extrapolations and utility data) were not implemented in the NCPE-adjusted base case, due to lack of robust data. These were explored in scenario analysis.

Results

The results of the Applicant and NCPE-adjusted base case deterministic cost-effectiveness analysis are presented in Tabl and Table 2, respectively. The Review Group highlight that several uncertainties exist in the Applicant and NCPE-adjusted base cases. These mainly pertain to long-term survival data and utility values. Changes, regarding these parameters, were not made in the NCPE-adjusted base. For the survival data, the most conservative choice was implemented for extrapolation OS and PFS in the Applicant base case. In the absence of more appropriate utility data, no changes were made. Results should therefore be interpreted with caution.

Table 1: Applicant base case incremental cost-effectiveness results [a,b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
HMRN SOC basket (n=90)	38,882	3.65	-	-	-
Zanubrutinib	321,176	6.37	282,294	2.72	103,811

ICER: incremental cost-effectiveness ratio; **QALY:** quality-adjusted life year; **HMRN:** Haematological Malignancy Research Network; **SOC:** standard-of-care.

[a] Corresponding probabilistic ICER using 1,000 iterations =€105,993/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes.

[b] A PAS applies to zanubrutinib, not included in this table.

Table 2: NCPE-adjusted base case incremental cost-effectiveness results [a,b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
HMRN SOC basket (n=73)	43,852	3.77	-	-	-
Zanubrutinib	323,128	6.34	279,276	2.57	108,662

ICER: incremental cost-effectiveness ratio; **QALY:** quality-adjusted life year; **HMRN:** Haematological Malignancy Research Network; **SOC:** standard-of-care.

[a] Corresponding probabilistic ICER using 1,000 iterations =€112,693/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes.

[b] A PAS applies to zanubrutinib, not included in this table

Sensitivity analysis

The probabilities of cost-effectiveness, for zanubrutinib versus the respective HMRN SOC baskets, in the Applicant and NCPE-adjusted base cases was 0% at thresholds of €20,000 per QALY and €45,000 per QALY. Deterministic one-way sensitivity analysis indicated that the most influential parameters in the model for both the Applicant and the NCPE-base case related to progression-free and progressed disease health-state utilities.

A price-ICER analysis, conducted using the NCPE-adjusted base case, indicated that a discount of 85.9% and 64.2% would be required for zanubrutinib to be considered cost-effective at a willingness-to-pay threshold of €20,000 per QALY and €45,000 per QALY, respectively.

4. Budget impact of zanubrutinib

The price to wholesaler for one pack (120 capsules) of zanubrutinib 80mg capsules is €5,334.71. Using NCPE preferred assumptions, the estimated total cost, per patient, per treatment course of zanubrutinib is €296,397 (including VAT).

The Applicant projected the market shares of zanubrutinib to be 20% in Year 1, increasing to

42% by Year 5. This resulted in two patients being treated in Year 1, increasing to 11 by Year 5. The Review Group noted that these market share estimates are associated with uncertainty as they are based on internal market assumptions only. The Applicant assumed that patients received a mean of 13.04 cycles (of 28 days) of zanubrutinib. No justification was provided for this assumption. The mean treatment duration of zanubrutinib estimated from the CEM, based on the Applicant base case TTD curve, was 5.64 years. According to the SmPC, and clinical opinion, treatment with zanubrutinib should be continued until disease progression or unacceptable toxicity. The Review Group therefore considered that mean treatment duration, derived from the CEM, better reflected the expected treatment duration in clinical practice. This treatment duration was applied in the NCPE-adjusted base case and capped at five years to align with the budget impact model forecast. This resulted in a mean of 65.22 cycles (of 28 days) of zanubrutinib in the NCPE-adjusted base case.

Based on this, in the NCPE-adjusted base case, the five-year cumulative gross drug-budget impact including VAT was €5.70 million, and the five-year cumulative net drug-budget impact including VAT was €5.65 million. Based on the Applicant's preferred assumption (13.04 cycles of zanubrutinib), the five-year cumulative gross drug-budget impact including VAT was €2.56 million, and the five-year cumulative net drug-budget impact including VAT was €2.50 million. The Review Group highlight that both the budget impact estimates are highly uncertain.

5. Patient Organisation submission

No Patient Organisation submissions were received over the course of the assessment.

6. Conclusion

The NCPE recommends that zanubrutinib (Brukinsa®) not be considered for reimbursement, for this indication, unless cost-effectiveness can be improved relative to existing treatments*.

** This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013*