

6.09 ZANUBRUTINIB, Capsule 80 mg, Brukinsa[®], Beigene Aus Pty Ltd.

1 Purpose of submission

- 1.1 The Category 2 submission requested a General Schedule Authority Required (Telephone/Streamlined) listing of zanubrutinib for the treatment of treatment naïve chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL).
- 1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus venetoclax + obinutuzumab.

Table 1: Key components of the clinical issue addressed in the submission

Component	Description
Population	Patients with previously untreated CLL and SLL who are inappropriate for fludarabine-based chemoimmunotherapy.
Intervention	Oral zanubrutinib 160 mg twice daily until disease progression or unacceptable toxicity.
Comparator	<ul style="list-style-type: none"> • Venetoclax + obinutuzumab (main comparator) • Acalabrutinib monotherapy (near-market comparator) • Acalabrutinib + obinutuzumab (near-market comparator)
Outcomes	Progression-free survival; overall response rate; overall survival; time to next treatment; safety.
Clinical claim	<p>In patients with previously untreated CLL/SLL who are unsuitable for fludarabine-based chemoimmunotherapy, zanubrutinib is:</p> <ul style="list-style-type: none"> • Non-inferior to venetoclax + obinutuzumab in terms of efficacy, with a non-inferior but different safety profile. • Non-inferior to acalabrutinib in terms of efficacy and safety. • Non-inferior to acalabrutinib + obinutuzumab in terms of efficacy and safety.

Source: Table 1-1, p16 of the submission.

Abbreviations: CLL = chronic lymphocytic leukaemia, SLL = small lymphocytic leukaemia

2 Background

- 2.1 A concurrent submission for zanubrutinib monotherapy for the treatment of relapsed/refractory CLL/SLL was considered at the March 2023 PBAC meeting.

Registration status

- 2.2 The submission was made under the TGA/PBAC Parallel Process. At the time of the evaluation for PBAC consideration, the Round 1 TGA clinical evaluation report was available. The TGA delegate's overview was received in January 2023. The ACM considered that the product has an overall positive benefit-risk profile for the indication: 'BRUKINSA is indicated as monotherapy for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL).'

Previous PBAC consideration

- 2.3 Zanubrutinib is listed on the PBS for the treatment of Waldenstrom macroglobulinaemia and mantle cell lymphoma.
- 2.4 The submission stated that a co-dependent application (MSAC application 1731) was submitted to the MSAC requesting a broadening of the eligible patient population for 17p deletion testing to include untreated CLL/SLL patients, as well as the addition of zanubrutinib to the list of drugs for which MBS Item 73343 can be used to determine PBS eligibility. This application was subsequently withdrawn on the basis that the proposed amendments would become redundant due to implementation of amendments to MBS Item 73343 associated with MSAC application 1544.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ZANUBRUTINIB					
zanubrutinib 80 mg capsule, 120	\$8,794.57 published price \$TBD effective price	1	120	5	Brukinsa
Category / Program: General Schedule					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)					
Episodicity: Untreated					
Condition: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)					
Indication: Untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)					
Treatment Phase: Initial, grandfathered, continuing					
Initial					
Clinical criteria (initial): The condition must be previously untreated					
AND					
Clinical criteria (initial): Patient must be inappropriate for fludarabine based chemo-immunotherapy					
AND					
Clinical criteria (initial): Patient must have a total cumulative illness rating scale (CIRS) score of greater than 6 (excluding CLL-induced illness or organ damage) OR Patient must have a creatinine clearance less than 70 mL/min					
AND					
Clinical criteria (initial): The treatment must be the sole PBS-subsidised therapy for this condition OR Clinical criteria (initial):					

Patient must have developed intolerance to another Bruton's tyrosine kinase (BTK) inhibitor or B-cell lymphoma 2 (BCL-2) inhibitor of a severity necessitating permanent treatment withdrawal when being treated for treatment naïve CLL/SLL.
Grandfather
Clinical criteria (grandfather):
Patient must have previously received non-PBS-subsidised treatment with this drug for untreated CLL/SLL prior to 1 Month 2023 [insert listing date here]
AND
Clinical criteria (grandfather):
The treatment must be the sole PBS-subsidised therapy for this condition
AND
Clinical criteria (grandfather):
Patient must not have developed disease progression while receiving treatment with this drug for this condition
Continuing
Clinical criteria (continuing):
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria (continuing):
Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition

Abbreviations: TBD = to be determined

- 3.1 The submission proposed a special pricing arrangement for zanubrutinib, with an effective price to be determined based on a cost-minimisation of zanubrutinib to venetoclax plus obinutuzumab, noting that venetoclax and obinutuzumab are subject to special pricing arrangements. As of 1 February 2023, obinutuzumab for CLL does not have special pricing arrangements.
- 3.2 The proposed restriction is narrower than the proposed TGA indication, which does not restrict treatment based on suitability for fludarabine-based chemoimmunotherapy, CIRS score/renal function, or limit use to patients with previously untreated disease.
- 3.3 The proposed initial treatment authority level and clinical criteria are generally consistent with the PBS listing for venetoclax for previously untreated CLL/SLL. However, the proposed restriction does not specify a creatinine clearance ≥ 30 mL/min, and also incorporates treatment of patients who have developed intolerance to another Bruton's tyrosine kinase (BTK) inhibitor or B-cell lymphoma 2 (BCL-2) inhibitor. There are currently no PBS-listed BTK inhibitors for patients with previously untreated CLL/SLL. The ESC considered it may also be appropriate to allow patients to be retreated with a BTKi if it is preceded by a gap of 12- or 24-months post first-line treatment. The ESC considered that retreatment with a BTKi should only be permitted under the PBS once (i.e., whether the same agent or another BTKi). The ESC acknowledged that there were no firm data regarding a time-frame for a recurrence-free period after which it would be appropriate to re-treat with an agent from the same class, or the clinical outcomes with retreatment.

- 3.4 The pre-PBAC response stated that the sponsor was open to clinician and PBAC advice on the proportion of patients that would be retreated, as the reasons for wanting to use sequential BTKi therapy could vary.
- 3.5 The proposed restriction does not include explicit criteria to assess the appropriateness for treatment with fludarabine-based chemoimmunotherapy, consistent with the existing restrictions for venetoclax + obinutuzumab. At the CLL clinician consultation meeting held in December 2022, the clinicians indicated that the existing PBS criteria around ‘inappropriate for fludarabine-based chemoimmunotherapy’ and ‘unsuitable for treatment with a purine analogue’ are no longer relevant to current clinical practice, and that fludarabine + cyclophosphamide + rituximab (FCR) is no longer a preferred regimen in any patient group (CLL Clinical Consultation Summary of Meeting, December 2022).
- 3.6 At the CLL clinician consultation meeting held in December 2022, the clinicians noted a significant access issue for young and/or fit patients who do not meet the existing PBS criteria for BTKi or venetoclax. The clinicians noted that, while the clinical need is highest in patients with poor risk cytogenetics, it would not be appropriate to limit access to BTKi and/or venetoclax therapy to these specific groups given the high clinical need across the broader young, fit population (CLL Clinical Consultation Summary of Meeting, December 2022). The ESC considered that it would be appropriate to remove the requirements for patients to be inappropriate for fludarabine-based chemoimmunotherapy, as well as the criteria for assessing suitability for fludarabine-based chemoimmunotherapy (CIRS score and creatinine clearance) from the requested restriction. The Pre-Sub-Committee Response (PSCR) and the pre-PBAC response stated that the sponsor accepts the removal of these additional criteria to align with the advice received from the clinical consultation. The pre-PBAC response suggested that approximately 27-35% of patients may meet the current criteria for treatment or retreatment with a purine analogue, and subsequently may access BTKi treatment. The PBAC considered that the use of fludarabine-based chemoimmunotherapy in CLL is low and declining and as such, there would be no increase in use associated with the restriction change.
- 3.7 The submission stated that the sponsor intends to commence a compassionate access program in January 2023, which would result in an estimated < 500 patients requiring grandfathered treatment with zanubrutinib. The Secretariat advised that the restriction could be simplified to a single restriction, with care taken so as to not inadvertently exclude such ‘grandfather’ patients. Specifically, ‘grandfather’ patients could continue treatment by the prescriber responding in the affirmative to the following Secretariat proposed parameter (provided all other criteria are met) on the first occasion a PBS prescription is written, which is the same criterion that every patient would continue through:

Treatment criteria:

Patient must be undergoing continuing treatment with this drug – the condition has not progressed whilst the patient has actively been on this drug

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 CLL and SLL are characterised by the progressive accumulation of functionally incompetent B lymphocytes in the peripheral blood, bone marrow and lymphoid tissues. In CLL, abnormal lymphocytes are predominantly found in blood, bone marrow and lymphoid tissue, whereas in SLL, abnormal lymphocytes are predominantly located in lymph nodes, bone marrow and other lymphoid tissue. Typical symptoms associated with CLL include swollen lymph nodes, pain, anaemia, infections, increased or unexplained bleeding/bruising, excessive nocturnal sweating, and unintentional weight loss.
- 4.2 The mean age at diagnosis for CLL in Australia is 71.0 years (males: 70.2 years; females: 72.4 years), with a five-year relative survival rate in 2014-2018 of 85.4% (AIHW, 2022). The disease is more common in men than women (62% versus 38%). Characteristics associated with a worse prognosis include more advanced disease stage, genetic factors (17p deletion/TP53 mutation, 11q deletion, unmutated IGHV), biochemical/cell surface markers (thymidine kinase, serum β 2 microglobulin), and patient characteristics (male sex, older age, worse ECOG performance score). Deletion of the short arm of chromosome 17 (17p deletion) is associated with resistance to conventional chemoimmunotherapy regimens (Hallek, 2015). 17p deletion is found in 5-8% of chemotherapy-naïve patients, but may also be acquired over time as patients undergo treatment.
- 4.3 In general, patients with asymptomatic early-stage disease, and selected patients with later-stage disease can be monitored without therapy until they have evidence of progressive or symptomatic disease (Hallek et al., 2018). The choice of therapy depends on several factors, including age, fitness, comorbidities, and the presence of prognostic genetic mutations.
- 4.4 Zanubrutinib is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK), a signalling molecule associated with the B-cell antigen receptor. In B-cells, BTK pathways are involved in B-cell proliferation, trafficking, chemotaxis, and adhesion.
- 4.5 The submission positioned zanubrutinib as an alternative to venetoclax + obinutuzumab and chlorambucil + obinutuzumab for patients with 17p deletion, and for patients without 17p deletion who are older/unfit.

5 Comparator

- 5.1 The submission nominated venetoclax + obinutuzumab as the main comparator. The main argument provided in support of this nomination was that venetoclax +

obinutuzumab is the treatment most likely to be replaced. The ESC considered venetoclax + obinutuzumab was an appropriate main comparator.

- 5.2 The submission identified acalabrutinib monotherapy and acalabrutinib + obinutuzumab as near market comparators. A resubmission for acalabrutinib + obinutuzumab for the treatment of patients with previously untreated CLL/SLL who are unsuitable for fludarabine-based chemoimmunotherapy was considered at the December 2022 intracycle PBAC meeting (December 2022 intracycle PBAC meeting agenda). The ESC considered that acalabrutinib monotherapy and acalabrutinib + obinutuzumab were appropriate near-market comparators. The PBAC noted that acalabrutinib, and acalabrutinib plus obinutuzumab, were appropriately nominated as near market comparators, however had not been recommended for listing.
- 5.3 The submission noted that a submission for ibrutinib, for use in combination with venetoclax in patients with previously untreated CLL/SLL, was to be considered at the November 2022 PBAC meeting. This submission was considered at the December 2022 intracycle PBAC meeting. The submission argued that ibrutinib + venetoclax is not a relevant comparator, due to the current lack of evidence around subsequent treatment options, and given that it is likely to be used in a different subset of patients compared to zanubrutinib due to its toxicity profile. The PBAC noted ibrutinib plus venetoclax was not recommended at the December 2022 meeting.
- 5.4 A submission for ibrutinib monotherapy, for the treatment of patients with previously untreated CLL/SLL who have 17p deletion received a positive recommendation at the November 2019 PBAC meeting (Paragraph 7.1, ibrutinib Public Summary Document (PSD), November 2019 PBAC meeting). However, at the time of the March 2023 PBAC meeting, ibrutinib was not listed on the PBS for the treatment of previously untreated CLL/SLL. At the November 2022 PBAC meeting, the positive recommendation was extended for a further 12 months (PBAC Outcomes, November 2022 PBAC meeting).

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (1), health care professionals (3), and from the four organisations, Haematology Society of Australia and New Zealand, Rare Cancers Australia, Lymphoma Australia, and the Leukaemia Foundation via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with zanubrutinib including the ease of taking zanubrutinib, efficacy, high tolerability, the potential for reduced hospital visits, and the opportunity for improved quality of life through the ability to return to work

and participate in the community. The PBAC noted that the consumer comments also described the difficulty of the 'watch and wait' approach for asymptomatic patients.

Clinical trials

- 6.3 The submission was based on the following comparisons of zanubrutinib to the nominated comparators:
- An unanchored unadjusted (naïve) indirect comparison and an unanchored matching-adjusted indirect comparison (MAIC) of zanubrutinib (SEQUOIA) versus venetoclax + obinutuzumab (CLL-14).
 - An unanchored unadjusted (naïve) indirect comparison and an unanchored MAIC of zanubrutinib (SEQUOIA) versus acalabrutinib (ELEVATE-TN).
 - An unanchored unadjusted (naïve) comparison of zanubrutinib (SEQUOIA) versus acalabrutinib + obinutuzumab (ELEVATE-TN).
- 6.4 A MAIC for zanubrutinib versus acalabrutinib + obinutuzumab was not presented in the submission. The submission stated that this was due to acalabrutinib + obinutuzumab being a comparator that is unique to the Australian setting. A MAIC of zanubrutinib versus acalabrutinib + obinutuzumab may have been informative to establish the relative efficacy of zanubrutinib versus combination therapy with acalabrutinib + obinutuzumab. Additionally, statistical testing for the difference between zanubrutinib versus acalabrutinib in the unanchored unadjusted (naïve) comparison was not presented. A resubmission for acalabrutinib + obinutuzumab was considered at the December 2022 intracycle PBAC meeting.
- 6.5 Details of the trial reports presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Zanubrutinib trials		
SEQUOIA (NCT03336333)	An international, Phase 3, open-label, randomized study of BGB-3111 compared with bendamustine plus rituximab in patients with previously untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma. Tam CS, Brown JR, Kahl BS, Ghia P, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. Tam CS, Robak T, Ghia P, Kahl BS, et al. Zanubrutinib monotherapy for patients with treatment naïve chronic lymphocytic leukaemia and 17p deletion.	Interim clinical study report, 6 January 2022. The Lancet Oncology 2022; 23(8):1031-1043). Haematologica 2020; 106(9): 2354-2363.
Venetoclax + obinutuzumab trials		
CLL-14 (NCT02242942)	Fischer K, Al-Sawaf O, Bahlo J, Fink AM, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. Al-Sawaf O, Zhang C, Tandon M, Sinha A, et al. Ven + obi versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. Al-Sawaf O, Zhang C, Lu T, Liao MZ, et al. Minimal residual disease dynamics after venetoclax-obinutuzumab treatment: extended off-treatment follow-up from the randomized CLL14 study. Al-Sawaf O, Gentile B, Devine J, Zhang C, et al. Health-related quality of life with fixed-duration venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: Results from the randomized, phase 3 CLL14 trial. Al-Sawaf O, Zhang C, Robrecht S, Kotak A, et al. S148 venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 5-year results of the randomized CLL14 study.	New England Journal of Medicine 2019; 380(23): 2225-2236. The Lancet Oncology 2020; 21(9):1188-1200. Journal of Clinical Oncology 2021; 39(36): 4049-4060. American Journal of Hematology 2021; 96(9): 1112-1119. HemaSphere 2022; 6(S3): 100-101.
Acalabrutinib +/- obinutuzumab trials		
ELEVATE-TN	Sharman JP, Egyed M, Jurczak W, Skarbnik A, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naïve chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. Sharman JP, Miklos E, Jurczak W, Skarbnik A et al. Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukemia. Sharman JP, Miklos E, Jurczak W, Skarbnik A et al. Acalabrutinib ± obinutuzumab versus obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukemia: five-year follow-up of ELEVATE-TN.	The Lancet 2020; 395(10232): 1278-1291. Leukemia 2022; 36:1171-1175. Journal of Clinical Oncology 2022; 40 (16_suppl): 7539.

Source: Table 2-3, pp37-38; Table 2-4, p39; Table 2-5, p40 of the submission.
Selected conference abstract citations omitted.

6.6 The key features of the SEQUOIA, CLL-14 and ELEVATE-TN trials are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Zanubrutinib versus bendamustine + rituximab					
SEQUOIA	590	Phase 3, randomised, open-label trial. Median duration of follow-up: 26.2 months	Unclear	<ul style="list-style-type: none"> • Age ≥65 years; or age 18-64 years with a CIRS score >6, CrCl <70 mL/min, or history of previous severe infection or multiple previous infections.^a • Confirmed presence of 17p deletion.^b • CD20+ CLL/SLL disease requiring treatment. • Measurable disease by CT/MRI • No prior systemic treatment for CLL/SLL. • ECOG score ≤2. • Life expectancy ≥6 months. 	<ul style="list-style-type: none"> • Progression-free survival • Overall response rate • Overall survival • Duration of response • MRD rate in 17p deletion cohort • Adverse events, • Quality of life (EORTC QLQ-C30, EQ-5D-5L).
Venetoclax + obinutuzumab versus chlorambucil + obinutuzumab					
CLL-14	432	Phase 3, randomised, open-label trial. Median duration of follow-up: 65.4 months (Al-Sawaf et al., 2022).	Unclear	<ul style="list-style-type: none"> - Age ≥18 years. - CIRS score >6 or CrCl <70 mL/min. - CLL disease requiring treatment. - Documented previously untreated CLL. - Life expectancy >6 months. 	<ul style="list-style-type: none"> • Progression-free survival • Overall response rate • Overall survival • MRD response rate • Duration of response • Time to next treatment • Event-free survival • Adverse events • Quality of life (MDASI, EORTC QLQ-C30, EQ-5D-5L).
Acalabrutinib versus acalabrutinib + obinutuzumab versus chlorambucil + obinutuzumab					
ELEVATE-TN	535	Phase 3, randomised, open-label trial. Median duration of follow-up: 58.2 months (Sharman et al., 2022).	Unclear	<ul style="list-style-type: none"> - Age ≥65 years or 18-64 years with a CIRS-Geriatric score >6 or CrCl of 30-69 mL/min). - Active CD20+ CLL disease requiring treatment. - No prior systemic treatment for CLL. - ECOG score ≤2. 	<ul style="list-style-type: none"> • Progression-free survival • Overall response rate • Overall survival • Time to next treatment • Adverse events • Quality of life (FACIT-Fatigue, EORTC QLQ-C30, EQ-5D-3L).

Source: Section 8, pp24-25; Section 9.3 pp31-34 of the SEQUOIA interim clinical study report; Section 3.4, p42-44; Section 4.1 pp44-47 of the CLL-14 trial protocol (Fischer et al., 2019); p6 of Sharman et al. (2020); pp9-11 of Sharman et al. (2020; supplementary appendix); Table 4, p14 of the November 2021 acalabrutinib Public Summary Document.

Abbreviations: CD = cluster of differentiation, CIRS = Cumulative Illness Rating Scale, CLL = chronic lymphocytic leukaemia, CrCl = creatinine clearance, CT = computerised tomography, ECOG = European Cooperative Oncology Group, EORTC = European Organisation for Research and Treatment of Cancer, FACIT = Functional Assessment of Chronic Illness Therapy, MDASI = MD Anderson Symptom Inventory, MRI = magnetic resonance imaging, MRD = minimal residual disease, QLQ = quality of life questionnaire, SLL = small lymphocytic leukaemia.

^a Patients who did not have 17p deletion were included in Cohort 1 and randomised to receive zanubrutinib or bendamustine + rituximab.

^b Patients who had 17p deletion were included in Cohort 2 and received zanubrutinib in a non-randomised fashion.

6.7 The SEQUOIA, CLL-14, and ELEVATE-TN trials had an unclear risk of bias. As the trials were open label, investigators, patients, and study personnel were not blinded to treatment allocation, which may have influenced the treatment of patients in the trial. Assessments made by study investigators (who were not blinded to treatment allocation) were at high risk of bias. Each trial included blinded assessments by an independent review committee, which had a lower risk of assessment bias. However,

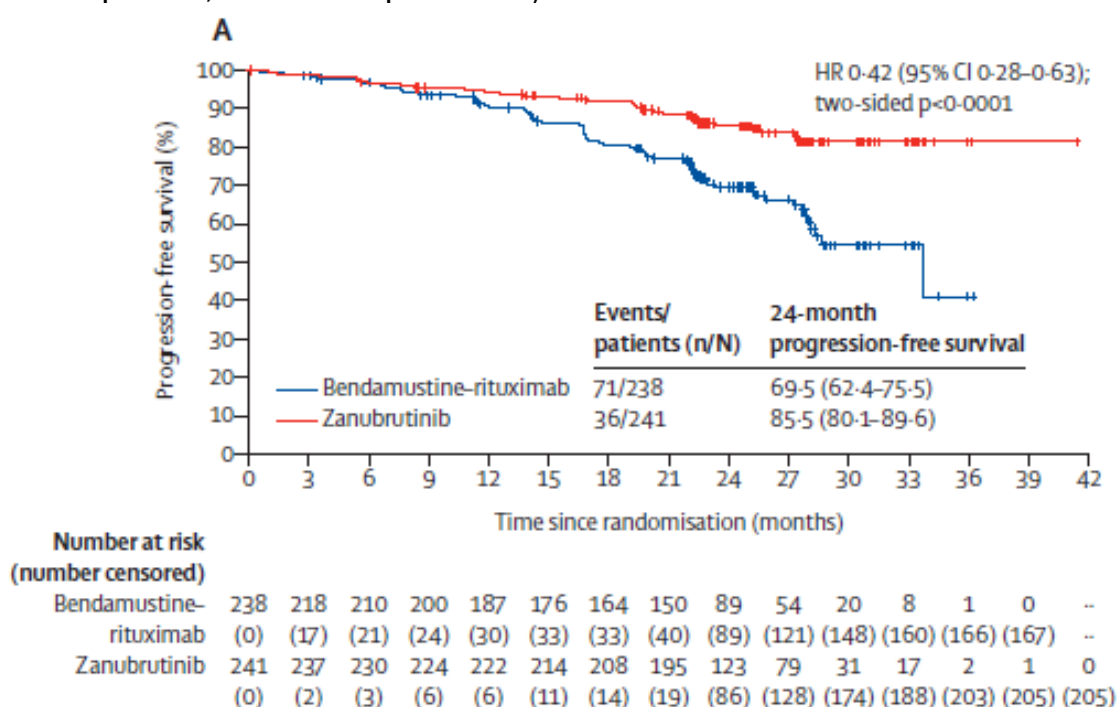
- longer term progression-free survival results reported in publications for the CLL-14 and ELEVATE-TN trials were based on investigator assessment.
- 6.8 The SEQUOIA trial included two main cohorts. Patients without 17p deletion (Cohort 1) were randomised to receive treatment with either zanubrutinib or bendamustine + rituximab. Patients with 17p deletion (Cohort 2) received treatment with zanubrutinib in a non-randomised fashion, on the basis that chemoimmunotherapy is not indicated for patients with 17p deletion due to poor response.
- 6.9 There were differences in eligibility criteria between the trials. The SEQUOIA trial included CLL and SLL patients, whereas the CLL-14 and ELEVATE-TN trials included patients with CLL only. Patients were eligible for the SEQUOIA trial if they were aged ≥ 65 years, or aged < 65 years and met additional criteria (creatinine clearance of 30 to 69 mL/min or a CIRS score > 6). Patients were eligible for the ELEVATE-TN trial if they were aged ≥ 65 years, or aged < 65 years and met additional criteria (creatinine clearance of 30 to 69 mL/min or a CIRS-Geriatric score > 6). Eligibility for the CLL-14 trial required all patients to have either a CIRS score > 6 or a creatinine clearance < 70 mL/min.
- 6.10 The median age of patients in the zanubrutinib (non-17p deletion) arm of the SEQUOIA trial was 70 years, and 64% of patients were male. Among patients with CLL, 14% had Binet Stage A (Stage B: 57%, Stage C: 29%). Among patients with SLL, 15% had Binet Stage A (Stage B: 60%, Stage C: 25%). Bulky disease (≥ 5 cm) was reported in 29% of patients. The ECOG score was 0 in 46% (1: 48%, 2: 6%), 52% had unmutated IGHV and 56% had a beta-2-microglobulin > 3.5 mg. Based on the pooled zanubrutinib arms used in the MAIC (i.e., patients with and without 17p deletion) 25% of patients had a CIRS score > 6 and 48% had a creatinine clearance < 70 mL/min.
- 6.11 There were differences between the trials in the duration of treatments. In the CLL-14 trial, treatment with venetoclax was based on a fixed treatment duration of 12 cycles (48 weeks), whereas treatment with zanubrutinib in the SEQUOIA trial and acalabrutinib in the ELEVATE-TN trial was ongoing until disease progression or unacceptable toxicity.
- 6.12 The PSCR stated that updated PFS and OS results from the SEQUOIA trial will be presented at an international conference in June 2023.
- 6.13 The submission argued that there are no previously accepted non-inferiority margins in this disease area, and that it can be difficult to conclusively establish non-inferiority in the context of small sample sizes of trials in the CLL, particularly in the absence of head-to-head data. The submission requested that the PBAC make a clinical judgement in consideration of the known limitations of MAIC analyses and low statistical power.

Comparative effectiveness

Unanchored unadjusted (naïve) indirect comparison of PFS and OS for the SEQUOIA, CLL-14 and ELEVATE-TN trials (median follow-up: 25.0 months, 28.1 months and 28.3 months, respectively)

6.14 Kaplan-Meier plots of independent review committee-assessed progression-free survival for patients without and patients with 17p deletion in the SEQUOIA trial are presented in Figure 1 and Figure 2, respectively.

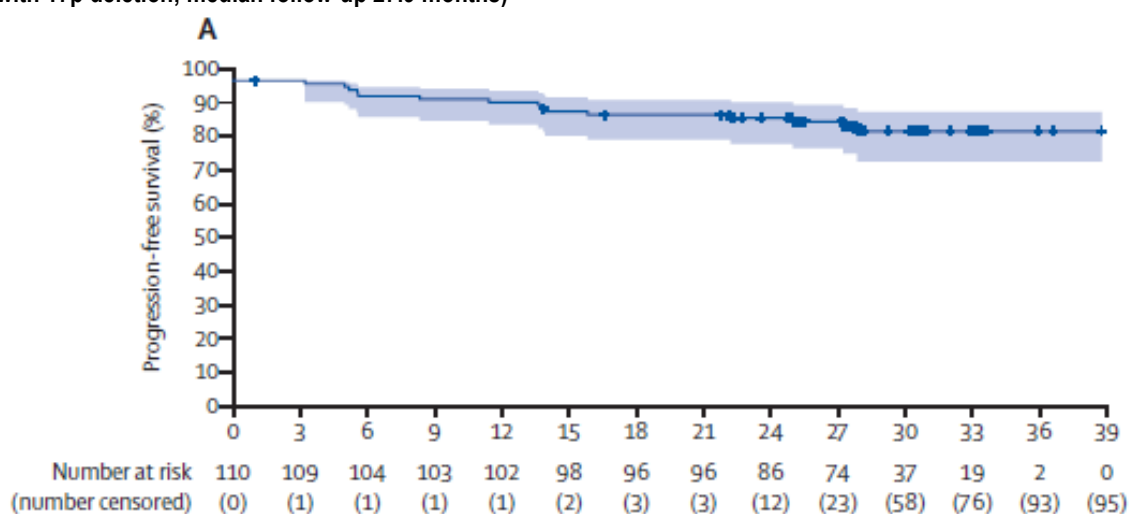
Figure 1: Independent review committee-assessed progression-free survival results for the SEQUOIA trial (patients without 17p deletion; median follow-up 25.0 months)



Source: Figure 2-8, p61 of the submission.

Abbreviations: CI = confidence interval, HR = hazard ratio

Figure 2: Independent review committee-assessed progression-free survival results for the SEQUOIA trial (patients with 17p deletion; median follow-up 27.9 months)



Source: Figure 2-9, p61 of the submission.

6.15 Table 4 presents a summary of independent review committee-assessed progression-free survival results for the SEQUOIA, CLL-14 and ELEVATE-TN trials.

Table 4: Independent review committee-assessed progression-free survival results for the SEQUOIA, CLL-14 and ELEVATE-TN trials

	SEQUOIA			CLL-14		ELEVATE-TN		
	ZANU N=241	ZANU (17p del) N=110	BEN + RIT N=238	VEN + OBI N=216	CHL + OBI N=216	ACAL + OBI N=179	ACAL N=179	CHL + OBI N=177
Median follow-up, months (range)	25.1 (0.0-41.4)	27.9 (1.0-38.8)	24.6 (0.0-36.2)	28.1 (0.0-35.9)		28.5 (1.7-40.3)	28.4 (0.1-40.8)	28.0 (0.0-40.4)
Events, n (%)	36 (14.9)	15 (13.6)	71 (29.8)	29 (13.4)	79 (36.6)	14 (7.8)	26 (14.5)	93 (52.5)
- Progression	27 (11.2)	14 (12.7)	59 (24.8)	14 (6.5)	71 (32.9)	9 (5.0)	20 (11.2)	82 (46.3)
- Death	9 (3.7)	1 (0.9)	12 (5.0)	15 (6.9)	8 (3.7)	5 (2.8)	6 (3.4)	11 (6.2)
Median PFS, months (95% CI)	NE (NE, NE)	NE (NE, NE)	33.7 (28.1, NE)	NE (NE, NE)	NE (31.1, NE)	NE (NE, NE)	NE (34.2, NE)	22.6 (20.2, 27.6)
HR vs comparator (95% CI)	0.42 (0.28, 0.63)	-	-	0.33 (0.22, 0.51)	-	0.1 (0.06, 0.17)	0.2 (0.13, 0.30)	-
KM estimate of PFS								
- 12 months, % (95% CI)	94.5 (90.8, 96.8)	93.6 (87.0, 96.9)	90.2 (85.4, 93.5)	94.6 (91.5, 97.7)	91.2 (87.3, 95.1)	95.9 (91.7, 98.0)	92.9 (87.8, 95.9)	84.6 (78.0, 89.3)
- 24 months, % (95% CI)	85.5 (80.1, 89.6)	88.9 (81.3, 93.6)	69.5 (62.4, 75.5)	88.6 (84.2, 93.0)	63.7 (57.0, 70.4)	92.7 (87.4, 95.8)	87.3 (80.9, 91.7)	46.7 (38.5, 54.6)

Source: Table 27, pp122-123; Table 18, pp100-101 of the SEQUOIA interim clinical study report; Table 4, p13 of the July 2020 acalabrutinib Public Summary Document; Table 4, p10 of the March 2020 venetoclax Public Summary Document.

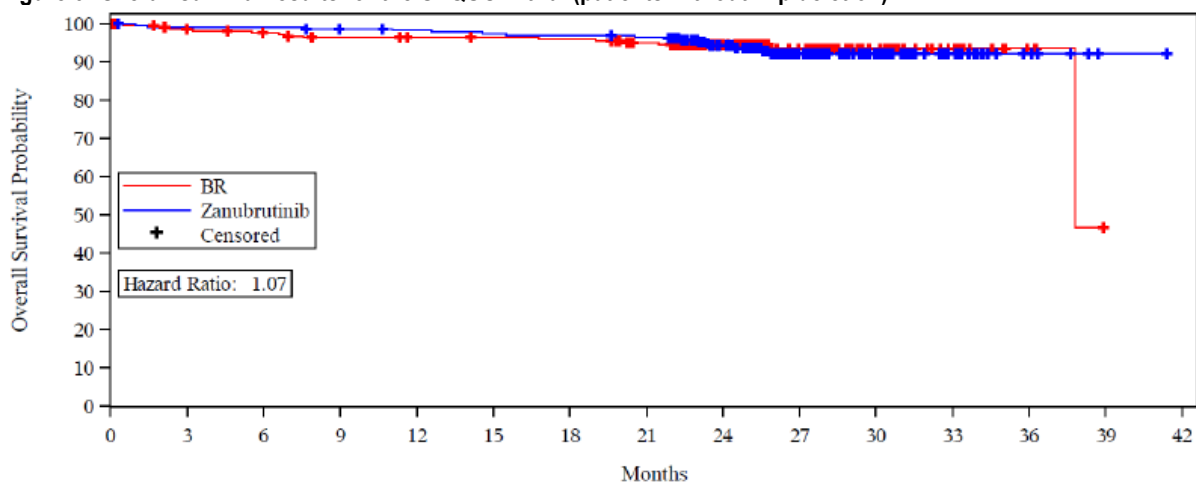
Abbreviations: ACAL = acalabrutinib, BEN = bendamustine, CHL = chlorambucil, CI = confidence interval, HR = hazard ratio, KM = Kaplan-Meier, NE = not estimable, NR = not reported, OBI = obinutuzumab, PFS = progression-free survival, RIT = rituximab, VEN = venetoclax, ZANU = zanubrutinib

6.16 Among patients without 17p deletion in the SEQUOIA trial, treatment with zanubrutinib was associated with a statistically significant improvement in progression free survival compared to bendamustine + rituximab (median progression-free survival not reached in either arm; hazard ratio = 0.42 [95% CI: 0.28, 0.63]). The

proportion of patients free from disease progression at 24 months was numerically higher in the zanubrutinib arms (without 17p deletion: 85.5%; with 17p deletion: 88.9%) compared to the bendamustine + rituximab arm (69.5%).

- 6.17 Based on an unanchored unadjusted (naïve) comparison of independent review committee-assessed progression-free survival at 24 months across the SEQUOIA, CLL-14 and ELEVATE-TN trials, the proportion of patients remaining free from disease progression was 85.5% for the zanubrutinib non-17p deletion arm, 88.9% for the zanubrutinib 17p deletion arm, 88.6% for the venetoclax + obinutuzumab arm, 87.3% for the acalabrutinib monotherapy arm, and 92.7% for the acalabrutinib + obinutuzumab arm.
- 6.18 Based on a median follow-up of 65.4 months, the proportion of patients free from disease progression at 60 months was 62.6% in the venetoclax + obinutuzumab arm of the CLL-14 trial (Al-Sawaf et al., 2022). Based on a median follow-up of 58.2 months, the proportion of patients free from disease progression at 60 months was 84% in the acalabrutinib + obinutuzumab arm and 72% in the acalabrutinib monotherapy arm of the ELEVATE-TN trial (Sharman et al., 2022). The results of a post hoc analysis of the ELEVATE-TN trial conducted at a median follow-up of 58.2 months (Sharman et al., 2022) were suggestive of a statistically significant difference in investigator-assessed progression-free survival in favour of acalabrutinib + obinutuzumab compared to acalabrutinib monotherapy (hazard ratio = 0.51 [95% CI: 0.32, 0.81]). The ESC considered that these results were supportive of the clinical claim of non-inferior efficacy of zanubrutinib when compared with venetoclax plus obinutuzumab, acalabrutinib plus obinutuzumab and acalabrutinib monotherapy with regards to progression free survival.
- 6.19 Kaplan-Meier plots of overall survival for patients without and patients with 17p deletion in the SEQUOIA trial are presented in Figure 3 and Figure 4, respectively.

Figure 3: Overall survival results for the SEQUOIA trial (patients without 17p deletion)

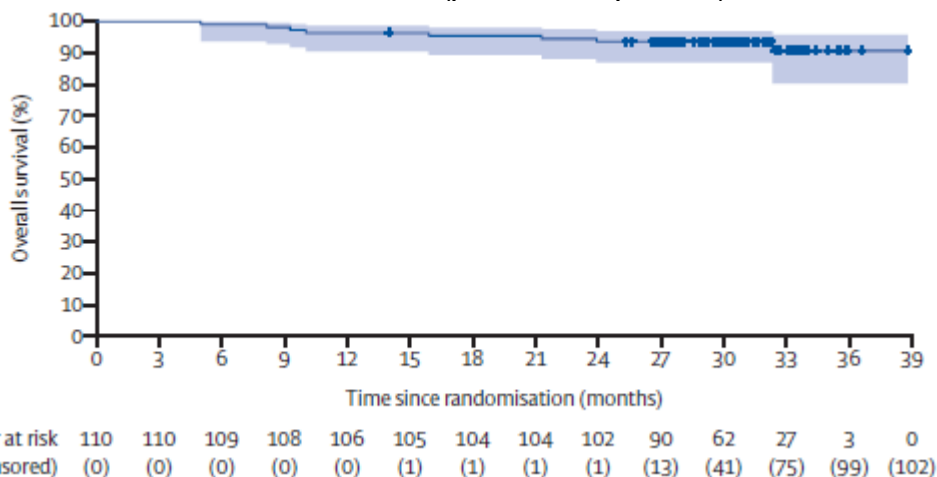


No. of Subjects at Risk		0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
BR	238	222	217	212	210	209	208	198	141	84	41	16	4	0		
Zanubrutinib	241	238	238	235	233	231	230	228	179	97	48	22	6	1	0	

Source: Figure 6, p111 of the SEQUOIA interim clinical study report.

Abbreviations: BR = bendamustine + rituximab.

Figure 4: Overall survival results for the SEQUOIA trial (patients with 17p deletion)



Source: Figure 2-12, pp65-66 of the submission.

6.20 Table 5 presents a summary of overall survival results for the SEQUOIA, CLL-14 and ELEVATE-TN trials.

Table 5: Overall survival results for the SEQUOIA, CLL-14 and ELEVATE-TN trials

	SEQUOIA			CLL-14		ELEVATE-TN		
	ZANU N=241	ZANU (17p del) N=110	BEN + RIT N=238	VEN + OBI N=216	CHL + OBI N=216	ACAL + OBI N=179	ACAL N=179	CHL + OBI N=177
Median follow-up, months (range)	26.5 (0.3-41.4)	30.4 (5.0-38.8)	25.1 (0.0-38.9)	28.1 (0.0-35.9)		28.5 (1.7-40.3)	28.4 (0.1-40.8)	28.0 (0.0-40.4)
Deaths, n (%)	16 (6.6)	8 (7.3)	14 (5.9)	20 (9.3)	17 (7.9)	9 (5.0)	11 (6.1)	17 (9.6)
Median OS, months (95% CI)	NE (NE, NE)	NE (NE, NE)	37.8 (37.8, NE)	NE (NR)	NE (NR)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
HR vs comparator (95% CI)	1.07 (0.51, 2.22)	-	-	1.24 (0.64, 2.40)	-	0.47 (0.21, 1.06)	0.60 (0.28, 1.27)	-
KM estimate of OS - 12 months, % (95% CI)	98.3 (95.6, 99.4)	96.4 (90.6, 98.6)	96.4 (93.0, 98.2)	93.3 (89.8, 96.7)	95.3 (92.4, 98.1)	96.1 (91.9, 98.1)	98.3 (94.8, 99.4)	96.5 (92.4, 98.4)
- 24 months, % (95% CI)	94.3 (90.4, 96.7)	93.6 (87.1, 96.9)	94.6 (90.6, 96.9)	91.8 (88.1, 95.5)	93.3 (90.0, 96.7)	94.9 (90.5, 97.3)	94.7 (90.2, 97.2)	91.7 (86.3, 95.0)

Source: Table 21, pp110-111; Table 31, p129 of the SEQUOIA interim clinical study report; Table 5, p12 of the March 2020 venetoclax Public Summary Document; Table 4, p15 of the July 2020 acalabrutinib Public Summary Document.

Abbreviations: ACAL = acalabrutinib, BEN = bendamustine, CHL = chlorambucil, CI = confidence interval, HR = hazard ratio, KM = Kaplan-Meier, NE = not estimable, NR = not reported, OBI = obinutuzumab, OS = overall survival, RIT = rituximab, VEN = venetoclax, ZANU = zanubrutinib

- 6.21 Among patients without 17p deletion in the SEQUOIA trial, there was no statistically significant difference in overall survival between the zanubrutinib and bendamustine + rituximab arms (median overall survival not reached in either arm; hazard ratio = 1.07 [95% CI: 0.51, 2.22]). Overall survival data for the SEQUOIA trial is immature.
- 6.22 Based on a naïve comparison of overall survival at 24 months across the SEQUOIA, CLL-14 and ELEVATE-TN trials, the proportion of patients remaining alive was 94.3% for the zanubrutinib non-17p deletion arm, 93.6% for the zanubrutinib 17p deletion arm, 91.8% for the venetoclax + obinutuzumab arm, 94.7% for the acalabrutinib monotherapy arm, and 94.9% for the acalabrutinib + obinutuzumab arm.
- 6.23 Based on a median follow-up of 65.4 months, the proportion of patients remaining alive at 60 months was 81.9% in the venetoclax + obinutuzumab arm of the CLL-14 trial (Al-Sawaf et al., 2022). Based on a median follow-up of 58.2 months, the proportion of patients remaining alive at 60 months was 90% in the acalabrutinib + obinutuzumab arm and 84% in the acalabrutinib monotherapy arm of the ELEVATE-TN trial (Sharman et al., 2022). The results of a post hoc analysis of the ELEVATE-TN trial conducted at a median follow-up of 58.2 months (Sharman et al., 2022) favoured the acalabrutinib + obinutuzumab arm, although the difference was not statistically significant (hazard ratio = 0.56 [95% CI: 0.31, 1.00]). The ESC considered these results were supportive of the clinical claim of non-inferior efficacy of zanubrutinib when compared with venetoclax plus obinutuzumab, acalabrutinib plus obinutuzumab and acalabrutinib monotherapy with regards to overall survival.

Other outcomes from the SEQUOIA, CLL-14 and ELEVATE-TN trials

- 6.24 Among patients without 17p deletion in the SEQUOIA trial, the overall response rate was 94.6% in the zanubrutinib arm and 85.3% in the bendamustine + rituximab arm. Among patients with 17p deletion, the overall response rate was 90.0%. The overall response rates for the acalabrutinib + obinutuzumab and acalabrutinib monotherapy arms in the ELEVATE-TN trial were 93.9% and 85.5%, respectively. Independent review committee-assessed overall response rate results were not available for the CLL-14 trial.
- 6.25 The median duration of response in the SEQUOIA trial was not reached in either zanubrutinib arm, and was 30.6 months in the bendamustine + rituximab arm. Among patients without 17p deletion, the event-free rate at 24 months was 87.5% for zanubrutinib and 70.3% for bendamustine + rituximab. Among patients with 17p deletion, the event-free rate at 24 months was 91.6%. Results for independent review committee-assessed duration of response were not available for the CLL-14 and ELEVATE-TN trials.
- 6.26 Results of quality of life outcomes for the SEQUOIA trial were available for the EORTC QLQ-C30 and the EQ-5D visual analogue scale. The change from baseline in the EORTC QLQ-C30 was statistically significant in favour of zanubrutinib at Week 24 for the global health score, physical function, nausea/vomiting, and diarrhoea compared with bendamustine + rituximab. Similar improvements in the EQ-5D visual analogue scale were observed in the zanubrutinib and bendamustine + rituximab arms at Week 12 and Week 24.
- 6.27 Results of quality of life outcomes for the CLL-14 trial were available for the EORTC QLQ-C30 and the MD Anderson Symptom Inventory (MDASI). The mean physical functioning and role functioning scores for the EORTC QLQ-C30 remained stable in both treatment arms at all time points. Improvement in the mean global health score was observed in both study arms with clinically meaningful improvements of ≥ 8 points in Cycle 3 in the venetoclax + obinutuzumab arm and Cycle 8 in the chlorambucil + obinutuzumab arm. Based on MDASI scores, CLL symptoms, core cancer symptoms, and symptom interference were generally low and comparable between treatment arms at baseline and were maintained throughout treatment and follow-up.
- 6.28 Results of quality of life outcomes for the ELEVATE-TN trial were available for the FACIT-Fatigue, EORTC QLQ-C30 and the EQ-5D visual analogue scale. Patients across all three arms showed improvements in the FACIT-Fatigue Global Fatigue Score that exceeded the nominated clinically important difference of 3 points. There were no statistically significant differences between groups for any of the FACIT-Fatigue domains. For the EORTC QLQ-C30, statistically significant differences favouring chlorambucil + obinutuzumab were noted for role functioning at Week 96, fatigue at Week 24 and diarrhoea at Week 24 compared to acalabrutinib + obinutuzumab, and for role functioning at Week 96 and diarrhoea at Week 24 compared to acalabrutinib

monotherapy. There were no statistically significant differences between groups for the EQ-5D visual analogue scale scores at Week 24 or Week 96.

Matching-adjusted indirect comparisons

- 6.29 The submission presented MAICs for zanubrutinib versus venetoclax + obinutuzumab and zanubrutinib versus acalabrutinib monotherapy for the outcomes of progression-free survival and overall survival. MAICs were not presented for safety outcomes.
- 6.30 Due to the lack of a common reference arm between the SEQUOIA and comparator trials, the MAICs were unanchored comparisons.
- 6.31 Results for zanubrutinib in the MAICs were based on pooled data for the zanubrutinib non-17p deletion and 17p deletion arms of the SEQUOIA trial. While pooling of the zanubrutinib arms resulted in a larger sample size, the inclusion of non-randomised patients with 17p deletion may have affected the reliability of the results. In particular, over 30% of patients in the pooled zanubrutinib population had 17p deletion. The presence of 17p deletion was a separate inclusion criterion in the SEQUOIA trial, and patients with 17p deletion did not need to meet the other specified age, CIRS score, creatinine clearance or previous infection criteria.
- 6.32 The submission stated that subgroup analyses comparing the treatment effect on progression-free survival across different levels of baseline factors were explored in publications for the ELEVATE-TN, CLL-14, ALLIANCE (ibrutinib +/- rituximab versus bendamustine + rituximab in previously untreated CLL) and RESONATE-2 (ibrutinib versus chlorambucil) trials, and in the SEQUOIA clinical study report.
- 6.33 Baseline factors were flagged as treatment effect modifiers if at least one of the studies detected a significant difference in the treatment effect across different factor levels. The following baseline factors were identified as treatment effect modifiers: IGHV mutation, cytogenetic mutation, β 2-microglobulin, ZAP-70 methylation, and CLL staging. The ESC considered these to be appropriate.
- 6.34 Baseline characteristics which demonstrated a numerical difference in treatment effects across different factor levels, but were not statistically significant, were flagged as potential treatment effect modifiers. These included bulky disease, age group, sex, geographic region, any cytopenia and complex karyotype.
- 6.35 The following variables that were not identified as either treatment effect modifiers or prognostic factors with effect modifier potential were flagged as prognostic factors: ECOG performance score, cancer type, time from initial diagnosis, ethnicity, cytopenia types and associated haematology results, creatinine clearance, lactate dehydrogenase, B-symptoms, CIRS score (standard or geriatric version) and tumour lysis syndrome risk. The ESC considered that CIRS score is not relevant in this situation as it is used to assess patients' suitability for treatment with chemoimmunotherapy.
- 6.36 The submission stated that to find the most optimal model, several sets of matching variables were explored. In the first step, the full set of mutually available factors were

used for matching and then, if necessary, the full set was further simplified by eliminating some factors based on their relevance until an optimal effective sample size was reached. If multiple descriptive statistics were available for the same factor, then an effort was made to adjust for the largest set of descriptive statistics for each, giving the highest priority to grouped ranges of values. Exclusion of potential treatment effect modifier or prognostic factors to preserve the effective sample size may not be a reasonable approach. Selective exclusion of variables is associated with a high risk of bias.

MAIC of zanubrutinib (SEQUOIA) versus venetoclax + obinutuzumab (CLL-14)

6.37 The technical document included three different MAIC models for zanubrutinib versus venetoclax + obinutuzumab based on alternative sets of matching variables (Models 1 to 3). A summary of the variables included for matching in each model, and the distribution of effect modifiers/prognostic variables before and after re-weighting were presented in the main body of the commentary. Results for Model 1 were presented in the submission and formed the basis for the clinical claim. The main difference between Model 1 and 2 was the exclusion of the CLL International Prognostic Index (CLL-IPI) from matching in Model 1. Model 3 was described as exploratory, and included CIRS score as a matching variable, along with exclusion of a number of other variables in order to preserve the effective sample size. No justification was provided in the submission for the selection of Model 1 compared to the other models.

6.38 Results for the MAICs of investigator-assessed progression-free survival and overall survival for Models 1 to 3 are presented in Table 6.

Table 6: Results for the MAICs of investigator-assessed progression-free survival and overall survival for zanubrutinib versus venetoclax + obinutuzumab

Model ^a	Hazard ratio (95% CI)
Investigator-assessed progression-free survival	
Naïve comparison (N = 352)	1.10 (0.69, 1.76)
Model 1 (ESS = 160.5)	1.01 (0.57, 1.81)
Model 2 (ESS = 155.1)	1.03 (0.57, 1.88)
Model 3 (ESS = 55.8)	0.90 (0.34, 2.38)
Overall survival	
Naïve comparison (N = 352)	0.75 (0.42, 1.34)
Model 1 (ESS = 160.5)	0.90 (0.45, 1.80)
Model 2 (ESS = 155.1)	0.88 (0.42, 1.81)
Model 3 (ESS = 55.8)	0.66 (0.21, 2.10)

Source: Table 11, p45; Table 17, p56; Table 31, p95; Table 32, p95 of the MAIC technical document, Attachment 4 of the submission.

Abbreviations: ESS = effective sample size, MAIC = matching adjusted indirect comparison

^a The submission presented the results for Model 1. Results for alternative models were included in the MAIC technical report.

6.39 Prior to adjustment of the MAIC (i.e., based on a naïve comparison of zanubrutinib and venetoclax + obinutuzumab), the hazard ratio for progression-free survival favoured venetoclax + obinutuzumab, but was not statistically significant (HR = 1.10 [95% CI: 0.69, 1.76]). After adjustment of the MAIC, the difference was not statistically

significant for Model 1, or for any of the other models included in the MAIC technical report.

- 6.40 Prior to adjustment of the MAIC (i.e., based on a naïve comparison of zanubrutinib and venetoclax + obinutuzumab), the hazard ratio for overall survival favoured zanubrutinib, but was not statistically significant (HR = 0.75 [95% CI: 0.42, 1.34]). After adjustment, the difference was not statistically significant for Model 1, or for any of the other models included in the MAIC technical report.
- 6.41 No non-inferiority margin for progression-free survival or overall survival were proposed in the submission. Inclusion of CIRS score >6 as a matching variable resulted in a large reduction in effective sample size, suggesting poor overlap between the trial populations. The results should be interpreted with caution due to the immaturity of the survival data for the SEQUOIA trial, the wide confidence intervals, and the risk of bias associated with selective exclusion of variables.

MAIC of zanubrutinib (SEQUOIA) versus acalabrutinib (ELEVATE-TN)

- 6.42 The technical document included five different MAIC models for zanubrutinib versus acalabrutinib based on alternative sets of matching variables (Models 1 to 5). A summary of the variables included for matching in each model, and the distribution of effect modifiers/prognostic variables before and after re-weighting are presented in the main body of the commentary. Results for Model 3 were presented in the submission and formed the basis for the clinical claim. No justification was provided in the submission for the selection of Model 3 compared to the other models.
- 6.43 Results for the MAICs of investigator-assessed progression-free survival and overall survival for Models 1 to 5 are presented in Table 7.

Table 7: Results for the MAICs of investigator-assessed progression-free survival and overall survival for zanubrutinib versus venetoclax + obinutuzumab

Model ^a	Hazard ratio (95% CI)
Investigator-assessed progression-free survival	
Naïve comparison (N = 352)	0.89 (0.55, 1.42)
Model 1 (ESS=132.5)	0.93 (0.52, 1.67)
Model 2 (ESS=107.5)	0.84 (0.46, 1.54)
Model 3 (ESS=159.8)	0.92 (0.53, 1.60)
Model 4 (ESS=124.5)	0.84 (0.46, 1.52)
Model 5 (ESS=136.4)	0.87 (0.50, 1.54)
Overall survival	
Naïve comparison (N = 352)	1.14 (0.56, 2.34)
Model 1 (ESS=132.5)	1.21 (0.50-2.89)
Model 2 (ESS=107.5)	1.05 (0.44-2.48)
Model 3 (ESS=159.8)	1.22 (0.56-2.65)
Model 4 (ESS=124.5)	1.08 (0.47-2.46)
Model 5 (ESS=136.4)	1.06 (0.48-2.37)

Source: Table 6, pp35-36; Table 28, p90 of the MAIC technical document, Attachment 4 of the submission.

Abbreviations: ESS = effective sample size, MAIC = matching adjusted indirect comparison

^a The submission presented the results for Model 1. Results for alternative models were included in the MAIC technical report.

- 6.44 Prior to adjustment of the MAIC (i.e., based on a naïve comparison of zanubrutinib and acalabrutinib), the hazard ratio for progression-free survival favoured zanubrutinib, but was not statistically significant (HR = 0.89 [95% CI: 0.55, 1.42]). After adjustment, the difference was not statistically significant for Model 3, or for any of the other models included in the MAIC technical report.
- 6.45 Prior to adjustment of the MAIC (i.e., based on a naïve comparison of zanubrutinib and acalabrutinib), the hazard ratio for overall survival favoured zanubrutinib, but was not statistically significant (HR = 1.14 [95% CI: 0.56, 2.34]). After adjustment in Model 3, the difference in overall survival between zanubrutinib and acalabrutinib remained not statistically significant (HR = 1.22 [95% CI: 0.56, 2.65]). After adjustment, the difference was not statistically significant for Model 3, or for any of the other models included in the MAIC technical report.
- 6.46 No non-inferiority margin for progression-free survival or overall survival were proposed in the submission. The evaluation stated the results of the MAICs for progression-free survival and overall survival should be interpreted with caution due to the immaturity of clinical data for the SEQUOIA trial, wide confidence intervals around the point estimates, and the risk of bias associated with selective exclusion of variables.

Comparative harms

- 6.47 Table 8 presents a comparison of safety outcomes for the SEQUOIA, CLL-14 and ELEVATE-TN trials based on a median follow-up of 25.9-30.5 months in the SEQUOIA trial, 28.1 months in the CLL-14 trial, and 28.0-28.5 months in the ELEVATE-TN trial.

Table 8: Comparison of reported adverse events for the SEQUOIA, CLL-14 and ELEVATE-TN trials

	SEQUOIA			CLL-14		ELEVATE-TN		
	ZANU N=240	ZANU (17p del) N=111	BEN + RIT N=227	VEN + OBI N=216	CHL + OBI N=216	ACAL + OBI N=179	ACAL N=179	CHL + OBI N=177
Median duration of follow-up, months (range)	26.4 (0.3-42.2)	30.5 (5.0-39.1)	25.9 (0.0-38.9)	28.1 (0.0-35.9)		28.5 (1.7-40.3)	28.4 (0.1-40.8)	28.0 (0.0-40.4)
Any AE, n (%)	224 (93.3)	109 (98.2)	218 (96.0)	200 (94.3)	213 (99.5)	171 (96.1)	170 (95.0)	167 (98.8)
Grade ≥3 AE, n (%) ^a	126 (52.5)	61 (55.0)	181 (79.7)	167 (78.8)	164 (76.6)	125 (70.2)	89 (49.7)	118 (69.8)
Serious AE, n (%)	88 (36.7)	45 (40.5)	113 (49.8)	104 (49.1)	90 (42.1)	69 (38.8)	57 (31.8)	37 (21.9)
AE leading to death, n (%)	11 (4.6)	3 (2.7)	12 (5.3)	16 (7.5)	8 (3.7)	4 (2.2)	6 (3.4)	10 (5.9)
Treatment discontinuation due to AE, n (%)	20 (8.3)	6 (5.4)	31 (13.7)	NR (16.0)	NR (15.4)	20 (11.2)	16 (8.9)	25 (14.1)
Treatment-related AE, n (%)	168 (70.0)	79 (71.2)	202 (89.0)	NR	NR	144 (80.9)	118 (65.9)	154 (91.1)
Grade ≥3 AE in >5%, n (%) ^a								
- Neutropenia	22 (9.2)	12 (10.8)	94 (41.4)	112 (52.8)	103 (48.1)	53 (29.8)	17 (9.5)	70 (41.4)
- Thrombocytopenia	4 (1.7)	1 (0.9)	16 (7.0)	29 (13.7)	32 (15.0)	15 (8.4)	5 (2.8)	20 (11.8)
- Anaemia	1 (0.4)	0 (0.0)	4 (1.8)	17 (8.0)	14 (6.5)	10 (5.6)	12 (6.7)	12 (7.1)
- Febrile neutropenia	2 (0.8)	1 (0.9)	17 (7.5)	11 (5.2)	8 (3.7)	3 (1.7)	2 (1.1)	9 (5.3)
- Infusion-related reaction	0 (0.0)	0 (0.0)	6 (2.6)	19 (9.0)	22 (10.3)	4 (2.2)	0 (0.0)	9 (5.3)
- Pneumonia	4 (1.7)	6 (5.4)	10 (4.4)	9 (4.2)	8 (3.7)	10 (5.6)	4 (2.2)	3 (1.8)
- Hypertension	15 (6.3)	5 (4.5)	11 (4.8)	NR	NR	5 (2.8)	4 (2.2)	5 (3.0)
- Neutrophil count decreased	5 (2.1)	5 (4.5)	24 (10.6)	NR	NR	2 (1.1)	0 (0.0)	5 (3.0)
Any AE in >15%, n (%)								
- Neutropenia	31 (12.9)	13 (11.7)	104 (45.8)	122 (57.5)	122 (57.0)	56 (31.5)	19 (10.6)	76 (45.0)
- Anaemia	11 (4.6)	6 (5.4)	43 (18.9)	35 (16.5)	40 (18.7)	21 (11.8)	25 (14.0)	20 (11.8)
- Diarrhoea	33 (13.8)	20 (18.0)	30 (13.2)	59 (27.8)	32 (15.0)	69 (38.8)	62 (34.6)	36 (21.3)
- Nausea	24 (10.0)	18 (16.2)	74 (32.6)	40 (18.9)	46 (21.5)	36 (20.2)	40 (22.3)	53 (31.4)
- Constipation	24 (10.0)	17 (15.3)	43 (18.9)	28 (13.2)	19 (8.9)	25 (14.0)	20 (11.2)	17 (10.1)
- Fatigue	28 (11.7)	10 (9.0)	36 (15.9)	32 (15.1)	30 (14.0)	50 (28.4)	33 (18.4)	29 (17.2)
- Pyrexia	17 (7.1)	8 (7.2)	60 (26.4)	48 (22.6)	33 (15.4)	23 (12.9)	12 (6.7)	35 (20.7)
- URTI	41 (17.1)	23 (20.7)	27 (11.9)	NR	NR	38 (21.3)	33 (18.4)	14 (8.3)
- Contusion	46 (19.2)	22 (19.8)	8 (3.5)	NR	NR	42 (23.6)	27 (15.1)	7 (4.1)
- Infusion-related reaction	1 (0.4)	0 (0.0)	43 (18.9)	95 (44.8)	110 (51.4)	24 (13.5)	0 (0.0)	67 (39.6)
- Arthralgia	32 (13.3)	22 (19.8)	20 (8.8)	NR	NR	39 (21.9)	28 (15.6)	8 (4.7)
- Rash	26 (10.8)	16 (14.4)	44 (19.4)	NR	NR	21 (11.8)	25 (14.0)	8 (4.7)
- Cough	27 (11.3)	14 (12.6)	23 (10.1)	34 (16.0)	25 (11.7)	39 (21.9)	33 (18.4)	15 (8.9)
- Headache	26 (10.8)	12 (10.8)	17 (7.5)	24 (11.3)	21 (9.8)	71 (39.9)	66 (36.9)	20 (11.8)
- Hypertension	29 (12.1)	10 (9.0)	20 (8.8)	NR	NR	13 (7.3)	8 (4.5)	6 (3.6)
- Thrombocytopenia	13 (11.7)	31 (13.7)	31 (12.9)	51 (24.1)	50 (23.4)	23 (12.9)	13 (7.3)	24 (14.2)

Source: Table 2-25, p71; Table 2-26, pp72-73 of the submission; Table 14.3.1.2.3.3.2, pp3754-3757 of the SEQUOIA clinical study report; Table 7, p17 of the March 2020 venetoclax Public Summary Document; Table 2, p2232 of Fischer et al. (2019); Table S6 of Fischer et al. (2019) supplementary appendix; Table 2, p27 of Sharman et al. (2020); Table S8, p30 of Sharman et al. (2020) supplementary appendix; Table 9, p19 of the acalabrutinib July 2020 Public Summary Document.

Abbreviations: ACAL = acalabrutinib, AE = adverse event, BEN = bendamustine, CHL = chlorambucil, NR = not reported, OBI = obinutuzumab, RIT = rituximab, ZANU = zanubrutinib

^a Grade 3 or 4 for the CLL-14 trial.

6.48 The most commonly reported treatment emergent adverse events in the zanubrutinib non-17p deletion and 17p deletion arms of the SEQUOIA trial were contusion, upper respiratory tract infection, diarrhoea, arthralgia, neutropenia, hypertension, cough, rash, headache, constipation and nausea.

- 6.49 The most commonly reported Grade ≥ 3 adverse events in the zanubrutinib non-17p deletion and 17p deletion arms of the SEQUOIA trial were neutropenia, hypertension, COVID-19, neutrophil count decreased, pneumonia and atrial fibrillation.
- 6.50 Based on a naïve comparison of the SEQUOIA, CLL-14 and ELEVATE-TN trials, almost all patients experienced at least one treatment emergent adverse event. The proportion of patients who experienced at least one Grade ≥ 3 adverse event (Grade 3 or 4 for the CLL-14 trial) was 52.5% and 55.0% for the zanubrutinib non-17p deletion and 17p deletion arms of the SEQUOIA trial, 78.8% for the venetoclax + obinutuzumab arm of the CLL-14 trial, and 70.2% and 49.7% for the acalabrutinib + obinutuzumab and acalabrutinib arms of the ELEVATE-TN trial.
- 6.51 The submission noted that zanubrutinib was associated with a lower incidence of Grade ≥ 3 neutropenia, thrombocytopenia, anaemia, leukopenia, febrile neutropenia, and a higher incidence of Grade ≥ 3 hypertension, atrial fibrillation and fall compared to venetoclax + obinutuzumab. The submission also noted the absence of Grade ≥ 3 infusion-related reactions among patients treated with zanubrutinib, which were reported in 9.0% of patients who received venetoclax + obinutuzumab. The submission argued that the naïve comparison of Grade ≥ 3 adverse events supports the conclusion of non-inferior but different adverse event profile for zanubrutinib versus venetoclax + obinutuzumab. The results of the naïve comparison should be interpreted with caution due to potential differences in patient populations that may have impacted the occurrence of adverse events, and differences in treatment durations for zanubrutinib compared to fixed duration venetoclax + obinutuzumab.
- 6.52 The submission claimed that the acalabrutinib monotherapy adverse events reported in the ELEVATE-TN trial were consistent with the adverse events for zanubrutinib reported in the SEQUOIA trial. The submission noted that while the incidences of headache and diarrhoea were higher in the acalabrutinib arm, zanubrutinib-treated patients had a higher incidence of hypertension. The ESC noted that adverse events were broadly similar between zanubrutinib and acalabrutinib.
- 6.53 The submission noted that acalabrutinib + obinutuzumab was associated with a higher incidence of Grade ≥ 3 adverse events compared to the zanubrutinib non-17p deletion/17p deletion arms of the SEQUOIA trial, including a higher incidence of Grade ≥ 3 neutropenia, thrombocytopenia, anaemia and infusion-related reactions.
- 6.54 The ESC noted that treatment discontinuations occurred less frequently in patients treated with zanubrutinib or acalabrutinib compared to venetoclax plus obinutuzumab, and that venetoclax plus obinutuzumab was associated with a higher incidence of neutropenia, anaemia, thrombocytopenia and diarrhoea compared to zanubrutinib.

Benefits/harms

- 6.55 A benefits and harms table was not presented as the submission made a claim of non-inferiority.

Clinical claim

- 6.56 The submission described zanubrutinib as non-inferior in terms of effectiveness compared with venetoclax + obinutuzumab, with a non-inferior but different safety profile. The evaluation considered this claim was not adequately supported:
- The clinical comparison was limited due to the absence of head-to-head clinical trials comparing zanubrutinib and venetoclax + obinutuzumab, and the lack of a common reference arm in the SEQUOIA and CLL-14 trials to facilitate an indirect comparison.
 - The results of the unanchored unadjusted (naïve) indirect comparisons of progression-free survival and overall survival may not be reliable due to differences in patient populations between the trials and the immaturity of the clinical evidence for zanubrutinib.
 - The results of the MAICs for progression-free survival and overall survival should be interpreted with caution due to the immaturity of clinical data for the SEQUOIA trial, wide confidence intervals around the point estimates, and the risk of bias associated with selective exclusion of variables for matching.
 - No non-inferiority margins for progression-free survival or overall survival were proposed in the submission. The lack of a statistically significant difference may not be sufficient to establish non-inferiority, as the 95% confidence intervals were wide and may include clinically important differences.
 - The results of the naïve safety comparison should be interpreted with caution due to potential differences in patient populations that may have impacted the occurrence of adverse events, and differences in treatment durations for zanubrutinib compared to fixed duration venetoclax + obinutuzumab.
- 6.57 The ESC acknowledged that the above concerns add uncertainty to the clinical comparison, however on balance, considered that the clinical claim of non-inferiority of zanubrutinib compared to venetoclax plus obinutuzumab was met.
- 6.58 The PBAC considered that the clinical claims of non-inferior effectiveness and safety for zanubrutinib versus venetoclax plus obinutuzumab were reasonably supported by the data, but with some uncertainty given the indirect treatment comparisons presented and the immaturity of the clinical evidence particularly for overall survival.
- 6.59 The submission described zanubrutinib as non-inferior in terms of effectiveness and safety compared to acalabrutinib. The evaluation considered this claim was not adequately supported:
- While zanubrutinib and acalabrutinib share the same mechanism of action, the clinical comparison was limited due to the absence of head-to-head clinical trials comparing zanubrutinib and acalabrutinib, and the lack of a common reference arm in the SEQUOIA and ELEVATE-TN trials to facilitate an indirect comparison.

- The results of the unanchored unadjusted (naïve) indirect comparisons of progression-free survival and overall survival may not be reliable due to differences in patient populations between the trials, and the immaturity of the clinical evidence for zanubrutinib.
- The results of the MAICs for progression-free survival and overall survival should be interpreted with caution due to the immaturity of clinical data for the SEQUOIA trial, wide confidence intervals around the point estimates, and the risk of bias associated with selective exclusion of variables for matching.
- No non-inferiority margins for progression-free survival or overall survival were proposed in the submission. The lack of a statistically significant difference may not be sufficient to establish non-inferiority, as the 95% confidence intervals were wide and may include clinically important differences.
- While the incidence of Grade ≥ 3 adverse events appeared broadly similar between zanubrutinib and acalabrutinib, the naïve safety comparison should be interpreted with caution due to potential differences in patient populations that may have impacted the occurrence of adverse events.

6.60 The submission described zanubrutinib as non-inferior in terms of effectiveness and safety compared to acalabrutinib + obinutuzumab. The evaluation considered this claim was not adequately supported:

- The clinical comparison was limited due to the absence of head-to-head clinical trials comparing zanubrutinib and acalabrutinib + obinutuzumab, and the lack of a common reference arm in the SEQUOIA and ELEVATE-TN trials to facilitate an indirect comparison. The submission did not present statistical testing for the difference between zanubrutinib versus acalabrutinib in the unanchored unadjusted (naïve) comparison, or a MAIC for zanubrutinib versus acalabrutinib + obinutuzumab.
- Based on a naïve comparison, a higher proportion of patients in the acalabrutinib + obinutuzumab arm of the ELEVATE-TN trial (92.7%) remained free from disease progression at 24 months compared to the zanubrutinib non-17p deletion arm of the SEQUOIA trial (85.5%). Treatment with acalabrutinib + obinutuzumab was associated with a numerically higher incidence of Grade ≥ 3 adverse events. However, the results of the naïve comparison should be interpreted with caution due to differences in patient populations between the trials, and the immaturity of the clinical evidence for zanubrutinib.
- It remains unclear whether combination therapy with a BTK inhibitor + a CD20 antibody will lead to improved survival outcomes compared to BTK inhibitor monotherapy. A post hoc analysis of results for the ELEVATE-TN trial conducted at a median follow-up of 58.2 months (Sharman et al., 2022) was suggestive of a statistically significant difference in investigator-assessed progression-free survival for acalabrutinib + obinutuzumab versus acalabrutinib monotherapy. A

higher proportion of patients in the acalabrutinib + obinutuzumab arm were alive at 60 months compared to the acalabrutinib monotherapy arm, although the difference in overall survival was not statistically significant.

Economic analysis

6.61 The submission presented a cost-minimisation of zanubrutinib versus venetoclax + obinutuzumab for patients with previously untreated CLL/SLL who are inappropriate for treatment with fludarabine-based chemoimmunotherapy. Key components of the cost-minimisation approach are summarised in Table 9.

Table 9: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	The submission claimed non-inferior effectiveness, based on evidence presented in the clinical evaluation.
Therapeutic claim: safety	The submission claimed non-inferior (but different) safety, based on evidence presented in the clinical evaluation.
Evidence base	Unanchored unadjusted (naïve) indirect comparison and unanchored MAIC of zanubrutinib (SEQUOIA trial) versus venetoclax + obinutuzumab (CLL-14).
Equi-effective doses	One initial and 8.67 continuing venetoclax scripts plus 7.355 obinutuzumab scripts are equivalent to 67.02 zanubrutinib scripts (69.6 months of treatment at a dose of 320 mg per day, assuming a mean dose intensity of 94.95%; i.e., 304 mg per day).* The cost-minimisation was conducted over 10 years.
Direct medicine costs	Venetoclax: \$1,645.30 (initial script) and \$7,623.02 (continuing script) ^a Obinutuzumab: \$5,028.35 per script ^a
Other costs or cost offsets	Obinutuzumab administration costs: \$1,256.20 * Obinutuzumab specialist visit costs: \$896.50 * Obinutuzumab premedication costs: \$15.82 * Venetoclax tumour lysis syndrome prophylaxis/monitoring costs: \$1,329.00

Source: Table 3-1, pp94-95 of the submission.

Abbreviations: MAIC, matching-adjusted indirect comparison.

^a Published prices. Venetoclax and obinutuzumab were both subject to special pricing arrangements (SPA) at the time of submission.

*Note: Revisions to these parameters were made in the pre-PBAC response. These revisions are not reflected in the table.

Estimation of number of doses of zanubrutinib

6.62 The treatment duration for zanubrutinib was estimated using extrapolated time to treatment discontinuation data based on pooled data for the zanubrutinib non-17p deletion and 17p deletion arms of the SEQUOIA trial. Based on an assumed time horizon of 10 years, a maximum treatment duration of 10 years was applied for zanubrutinib.

6.63 Individual patient level data for pooled time to treatment discontinuation were fitted with six parametric models (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma distributions). Models were assessed using Akaike information criteria (AIC) and Bayesian information criteria (BIC) statistics, as well as visual inspection of fitted parametric models and Kaplan-Meier curves. The submission stated that an exponential parametric model was selected on the basis that it had the lowest AIC and BIC, the best visual fit, and to reflect the clinical association between time to treatment discontinuation and progression-free survival.

- 6.64 The submission stated that progression-free survival data for the venetoclax + obinutuzumab arm of the CLL-14 trial was used to cap time to treatment discontinuation for zanubrutinib to ensure that the predicted time to treatment duration survival rates were aligned with the progression-free survival of venetoclax + obinutuzumab, and to prevent implausible time to treatment discontinuation extrapolation. This assumption was considered uncertain. Progression-free survival associated with fixed treatment duration venetoclax + obinutuzumab in the CLL-14 trial may not be a suitable proxy for progression-free survival for ongoing treatment with a BTK inhibitor. The pre-PBAC response agreed to remove the survival capping from the model.
- 6.65 Extrapolation of progression-free survival for the venetoclax + obinutuzumab arm was conducted using progression-free survival data for the CLL-14 trial reported at a median follow-up of 52.4 months (Al-Sawaf et al., 2021). The submission stated that an exponential parametric model was selected on the basis that it had the lowest BIC, the best visual fit, and was specified as the preferred parametric model in the March 2020 venetoclax + obinutuzumab submission (Paragraph 6.44, venetoclax, PSD, March 2020 PBAC meeting).
- 6.66 A discount rate of 5% was applied to the adjusted zanubrutinib time to treatment discontinuation survival data. The PBAC previously considered that it would be appropriate to apply discounting at 5% per annum to costs in the cost-minimisation of onasemnogene abeparvovec versus nusinersen (Paragraph 8.11, onasemnogene abeparvovec, PSD, September 2021 PBAC meeting).
- 6.67 Based on the extrapolated time to treatment discontinuation data, with capping based on the extrapolated venetoclax + obinutuzumab progression-free survival curve and a discount of 5% applied, the submission estimated a mean treatment duration for zanubrutinib of 69.62 months, equating to 70.6 scripts (based on $69.62 \div 12 \times [365/30] = 70.6$ scripts). A dose intensity of 94.95% was then applied, based on the weighted average dose intensity for the zanubrutinib non-17p deletion (94.85%) and 17p deletion (95.16%) arms of the SEQUOIA trial, resulting in an estimate of 67.02 zanubrutinib scripts per course. It is unclear whether the derived treatment duration and applied dose intensity will reflect the treatment duration and dose intensity for zanubrutinib in Australian clinical practice. The pre-PBAC response agreed to remove the survival capping from the model. The PBAC noted this increased the mean treatment duration for zanubrutinib from 69.62 months to 70.73 months (71.7 scripts or 68.09 scripts accounting for dose intensity).

Estimation of number of doses of venetoclax + obinutuzumab

- 6.68 The number of venetoclax (1 initial and 8.67 continuing scripts) and obinutuzumab scripts (7.355) per course was based on the mean number of venetoclax and obinutuzumab scripts reported for the venetoclax + obinutuzumab arm of the CLL-14 trial (Paragraph 5.31, venetoclax, PSD, July 2020 PBAC meeting). No dose intensity adjustment was applied to venetoclax or obinutuzumab, which may not be reasonable

given that a dose intensity adjustment was included for zanubrutinib. The PSCR stated that the dose intensity for venetoclax + obinutuzumab used in the submission was based on what was accepted by the PBAC in its previous consideration of this therapy (Paragraph 5.31, venetoclax, PSD, July 2020 PBAC meeting). Given the one-year fixed duration and mode of administration for venetoclax + obinutuzumab treatment, the PSCR stated that dose intensity is expected to be higher than with a long-term oral therapy, such as zanubrutinib, that is administered over a 10-year time horizon.

Equi-effective doses

6.69 The submission proposed the following equi-effective doses:

- One initial and 8.67 continuing venetoclax scripts plus 7.355 obinutuzumab scripts are equivalent to 69.62 months of zanubrutinib treatment at a dose of 304 mg daily (67.02 zanubrutinib scripts).

6.70 The pre-PBAC response proposed the following equi-effective doses:

- One initial and 8.67 continuing venetoclax scripts plus 7.355 obinutuzumab scripts are equivalent to 70.73 months of zanubrutinib treatment at a dose of 304 mg daily (68.09 zanubrutinib scripts).

6.71 Table 10 summarises the cost offsets included in the cost-minimisation.

Table 10: Cost offsets included in the cost-minimisation

Characteristic	Cost per patient (10-year time horizon)	Source
Obinutuzumab IV infusion costs *	\$1,256.20	Infusion cost based on MBS 13950 (\$114.20), assuming 11 infusions per course of obinutuzumab.
Obinutuzumab specialist visit costs *	\$896.50	Specialist visit cost based on MBS 116 (\$81.05). One specialist visit per infusion with obinutuzumab, assuming 11 infusions per course of obinutuzumab ^a
Obinutuzumab premedication costs *	\$15.82	Based on the published AEMPs for paracetamol 500 mg tablets (1746X; \$1.53), dexamethasone 4 mg tablets (2507Y; \$4.84), and loratadine 10 mg tablets (4313B; \$18.04). Assuming two paracetamol tablets, five dexamethasone tablets and one loratadine tablet per infusion (total \$1.44), and 11 infusions per course.
Venetoclax TLS prophylaxis/monitoring costs	\$1,329.00	Cost of TLS prophylaxis per patient (\$1,222) based on July 2020 venetoclax submission (Paragraph 5.32, venetoclax, PSD, July 2020 PBAC meeting), inflated from Year 2019 to 2023 using an online cost converter tool.

Source: Section 3.4, pp101-103 of the submission; 'Section 3_TN CLL' Excel workbook.

Abbreviations: AEMP = approved ex-manufacturer price; IV = intravenous, MBS = Medicare Benefits Schedule, PSD = Public Summary Document, TLS = tumour lysis syndrome

^a The MBS Item cost (\$81.05) was erroneously specified as \$81.50 in the cost-minimisation spreadsheet.

* Revisions to these parameters were made in the pre-PBAC response. These revisions are not reflected in the table.

6.72 The assumed cost offsets appeared to be overestimated due to the following reasons:

- The number of infusions used to derive the obinutuzumab infusion, specialist visit and premedication costs (11) was an overestimate. A maximum of 9 obinutuzumab infusions would be required (assuming 100 mg on Day 1, 900 mg on Day 2, and 1,000 mg on Days 8 and 15 of Cycle 1; and 1,000 mg on Day 1 of

Cycles 2-6). However, the actual number of infusions in clinical practice would be lower given that not all patients would receive all infusions. The ESC agreed with the evaluation. The PSCR stated that the number of infusions used to derive these costs reflects what the PBAC accepted for venetoclax plus obinutuzumab (Paragraph 5.31, venetoclax, PSD, July 2020 PBAC meeting). The PSCR stated that the results of the cost-minimisation were not highly sensitive to changes in these inputs.

- The assumption that all patients would require a specialist visit prior to administration of obinutuzumab may not be reasonable.
- The eviQ guidelines state that the antihistamine premedication and intravenous corticosteroid premedication may be omitted for subsequent obinutuzumab infusions if no infusion-related reactions occurred with the previous infusion (note that the submission included costs of dexamethasone tablets, whereas the eviQ treatment protocol specifies parenteral dexamethasone).
- While the risk of tumour lysis syndrome with zanubrutinib is low, tumour lysis syndrome costs associated with prophylaxis/monitoring may be applicable to some patients treated with zanubrutinib (i.e., patients with high tumour burden). The PSCR stated that in an analysis of patients treated with zanubrutinib, only two of 1,550 patients (0.1%) experienced tumour lysis syndrome during zanubrutinib monotherapy treatment. Based on these data coupled with advice received from key opinion leaders, the PSCR argued that it is unlikely that routine tumour lysis syndrome monitoring will be undertaken for most patients receiving zanubrutinib in practice.

- 6.73 The pre-PBAC response agreed to halve the number of infusions, specialist visits and premedication costs. The PBAC considered that this was appropriate, noting that the cost-minimised price presented in the pre-PBAC response had been derived by applying a reduction of 75% in some cases, and therefore required adjusting.
- 6.74 Table 11 presents the derivation of the cost-minimised price for zanubrutinib based on the published prices of venetoclax and obinutuzumab. The cost-minimised price in Table 11 does not include the changes proposed in the pre-PBAC response as specified in paragraphs 6.64, 6.67 and 6.73.

Table 11: Derivation of the cost-minimised price for zanubrutinib based on the published prices of venetoclax and obinutuzumab

	VEN + OBI	ZANU
Proposed equi-effective dose	Venetoclax: 1 initial script; 8.67 continuing scripts. Obinutuzumab: 7.355 scripts	67.02 scripts
Treatment cost (venetoclax + obinutuzumab)		
VEN drug cost over 10 years - AEMP ([1 x \$1,645.30] + [8.67 x \$7,623.02])	\$67,736.88	-
VEN tumour lysis syndrome prophylaxis costs	\$1,329.00	-
OBI drug cost over 10 years - AEMP (7.355 x \$5,028.35)	\$36,983.51	-
OBI administration cost – MBS 13950 (11.0 x \$114.20)	\$1,256.20	-
OBI specialist visits (11.0 x \$81.50) ^a	\$896.50	-
OBI premedication costs (11.0 x \$1.44)	\$15.82	-
VEN + OBI total treatment costs over 10 years	\$108,217.92	-
Cost-minimisation (zanubrutinib)		
ZANU total treatment costs over 10 years	-	\$ [REDACTED]
ZANU cost per script - AEMP (\$ [REDACTED] ÷ 67.02 scripts)	-	\$ [REDACTED]
ZANU cost per script - DPMQ	-	\$ [REDACTED] ^b

Source: 'Results' tab of the Section 3_TN CLL Excel workbook.

Abbreviations: AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity, OBI = obinutuzumab, VEN = venetoclax

^a An MBS cost of \$81.50 was included per specialist visit, whereas the specified MBS cost is \$81.05.

^b Error in application of AHI markup corrected during the evaluation, resulting in a DPMQ of \$ [REDACTED], compared to \$ [REDACTED] presented in the submission.

- 6.75 Based on the published prices of venetoclax and obinutuzumab, the estimated cost-minimised DPMQ for zanubrutinib as detailed in Table 11 was \$ [REDACTED].
- 6.76 Table 12 presents the results of sensitivity analyses for the cost-minimisation of venetoclax + obinutuzumab and zanubrutinib. The cost-minimised price in Table 12 does not include the changes proposed in the pre-PBAC response as specified in paragraphs 6.64, 6.67 and 6.73.

Table 12: Sensitivity analyses for the cost-minimisation of zanubrutinib versus venetoclax + obinutuzumab (based on published prices)

	Cost-minimised ZANU AEMP	% change from base case
Base case	\$	-
Time horizon (base case: 10 years) <ul style="list-style-type: none"> • 15 years • 12.5 years • 7.5 years • 5 years 	\$ \$ \$ \$	-16% -10% 18% 54%
Discount rate (base case: 5% applied to zanubrutinib TTD) <ul style="list-style-type: none"> • 0% • 3.5% 	\$ \$	-19% -6%
Zanubrutinib TTD (base case: exponential function, capped based on VEN + OBI PFS exponential function) <ul style="list-style-type: none"> • Exponential function, PFS cap removed • Log-logistic function, PFS cap removed • Gompertz function, PFS cap removed 	\$ \$ \$	-2% -1% -9%
Cost offsets (base case: included) <ul style="list-style-type: none"> • Excluded 	\$	-3%

Source: Table 3-9 of the submission; additional sensitivity analyses conducted using the 'Section 3_TN CLL' Excel workbook.
 Abbreviations: AEMP = approved ex-manufacture price, OBI = obinutuzumab, PFS = progression-free survival, TTD = time to treatment discontinuation, VEN = venetoclax, ZANU = zanubrutinib

6.77 The results of the cost minimisation were most sensitive to changes in the time horizon and removal of the discount rate applied to the zanubrutinib time to treatment discontinuation.

Drug cost/patient/course

6.78 Table 13 presents a comparison of drug costs for zanubrutinib and venetoclax + obinutuzumab included in the economic model and financial estimates. The cost per script and the treatment duration for the cost-minimisation and the financial estimates in Table 13 does not include the changes specified in paragraphs 6.64, 6.67 and 6.73.

Table 13: Drug cost per patient for zanubrutinib and venetoclax + obinutuzumab

	Clinical study	Cost-minimisation	Financial estimates
Zanubrutinib			
Cost per script (DPMQ)	-	\$ ^a	\$8,794.57 ^b
Treatment duration	Zanubrutinib non-17p arm: 26.4 months ^c Zanubrutinib 17p arm: 25.9 months ^c	69.6 months ^d	70 months ^{e,f}
Dose intensity	Zanubrutinib non-17p arm: 94.85% Zanubrutinib 17p arm: 95.16%	94.95% ^g	100%
Cost per course	-	\$	\$615,619.90
Venetoclax + obinutuzumab			
VENETOCLAX			
Cost per script	-	Starter pack (AEMP): \$1,645.30 Continuing pack (AEMP): \$7,623.02	Starter pack (DPMQ): \$1,791.55 Continuing pack (DPMQ): \$7,784.30
Compliance ^h	Starter pack: 1 Continuing pack: 8.67	Starter pack: 1 Continuing pack: 8.67	Starter pack: 1 Continuing pack: 8.67
Cost per course	-	\$67,736.88 (AEMP)	\$69,281.43 (DPMQ)
OBINUTUZUMAB			
Cost per script	-	\$5,028.35 (AEMP)	\$5,193.79 (weighted DPMA) ⁱ
Compliance	7.355 scripts/course	7.355 scripts/course	7.355 scripts/course
Cost per course	-	\$36,983.51 (AEMP)	\$38,200.32 (weighted DPMA) ⁱ

Source: 'Section4_TN CLL' Excel workbook; Section 3_TN CLL Excel workbook.

Abbreviations: AEMP = approved ex-manufacturer price, DPMA = dispensed price for maximum amount, DPMQ = dispensed price for maximum quantity

^a Cost-minimised DPMQ for zanubrutinib based on the published prices of venetoclax and obinutuzumab, with incorrect application of AHI markup corrected during the evaluation.

^b Proposed published price of zanubrutinib.

^c Median treatment duration at the interim analysis.

^d Derived from extrapolated time to treatment discontinuation for zanubrutinib in the SEQUOIA trial, capped based on venetoclax + obinutuzumab progression-free survival in the CLL-14, applying a 5% discount to time to treatment discontinuation, and assuming a maximum 10-year treatment period.

^e While a treatment duration of 70 months was assumed, the submission assumed that treatment was distributed over 7.39 years (i.e., 1 ÷ 13.5% = 7.39).

^f The submission assumed 70 calendar months of treatment would equate to 70 zanubrutinib scripts. However, based on a pack size of 30 days' supply, 70 months of treatment would equate to 71.02 packs $[(365.25 \div 12 \times 70) \div 30] = 71.02$.

^g Weighted average dose intensity for the zanubrutinib non-17p deletion and 17p deletion arms.

^h Based on a treatment duration of 288.1 days reported for the venetoclax + obinutuzumab arm of the CLL-14 trial in the venetoclax July 2020 Public Summary Document, assuming 28 days of initial treatment and 260.1 days of continuing treatment, and 100% treatment compliance.

ⁱ Based on a 30.05%:69.95% public/private hospital split.

Estimated PBS usage & financial implications

6.79 This submission was not considered by DUSC. The submission used a market share approach to estimate the utilisation and financial impacts of listing zanubrutinib for the treatment of patients with previously untreated CLL/SLL who are inappropriate for fludarabine-based chemoimmunotherapy.

6.80 The sources of data used in the financial estimates are presented in Table 14.

Table 14: Key inputs for the financial estimates

Parameter	Value applied and source	Comment
Annual venetoclax initial treatment scripts	389; PBS dispensing data for Item 12188L (January to December 2021).	Venetoclax for use in combination with obinutuzumab was listed on the PBS in December 2020. The available PBS data for venetoclax and obinutuzumab in 2021 does not represent the full treatment course for some patients (i.e., patients who would have initiated treatment from January 2020 to November 2020 and continued into 2021 had venetoclax + obinutuzumab been listed). The relative proportion of venetoclax and obinutuzumab scripts (2,649 and 2,757, respectively) did not reflect the relative proportion of venetoclax and obinutuzumab scripts assumed in the cost-minimisation (9.67 and 7.355). Additionally, the implied number of venetoclax + obinutuzumab patients per year (318) was lower than the number of venetoclax initial treatment scripts (389).
Annual venetoclax continuing scripts	2,260; PBS dispensing data for Item 12199C and 12205J (January to December 2021).	
Annual obinutuzumab scripts	2,757; PBS dispensing data for Item 12193R and 12204H (January to December 2021).	
Zanubrutinib uptake rate	Year 1-6: 40%. Sponsor assumption that 40% of venetoclax and obinutuzumab scripts would be replaced by zanubrutinib.	Uptake of zanubrutinib may be higher than estimated, given that zanubrutinib is an oral treatment, current clinical evidence may be suggestive of improved progression-free survival for continuous treatment with BTK inhibitor versus fixed duration treatments, and current PBS limitations on retreatment with venetoclax in the event of disease progression. The PSCR and the pre-PBAC response stated that the assumed uptake rate in Years 1 to 6 of listing (40%) was likely to be optimistic.
Grandfathered patients	█ ¹ ; Sponsor estimate. The submission stated that the sponsor intends to commence a compassionate access program in January 2023, which would result in an estimated █ ¹ patients requiring grandfathered treatment with zanubrutinib.	Grandfathered patients are likely to be included in the market share estimates of prevalent patients and may have been double counted in the submission. The PBAC considered the grandfathered patients would already be accounted for given the prevalence approach used.
Zanubrutinib treatment duration	70 months. Estimated from zanubrutinib time to treatment discontinuation data for the SEQUOIA trial, extrapolated using an exponential function, with capping based on extrapolated venetoclax + obinutuzumab progression-free survival from the CLL-14 trial.	The estimated mean treatment duration for zanubrutinib was considered uncertain. The application of a 5% discount to time to treatment discontinuation may not be reasonable for deriving the estimated financial implications to the PBS. The submission assumed 70 calendar months of treatment would equate to 70 zanubrutinib scripts. However, based on a pack size of 30 days' supply, 70 months of treatment would equate to 71.02 packs ($[365.25 \div 12 \times 70] \div 30 = 71.02$). The pre-PBAC response provided a revised estimate of the treatment duration based on changes as detailed in paragraphs 6.64, 6.67 and 6.73. The PBAC considered discounting should not be applied for the financial estimates.
Venetoclax scripts per patient	1 initial script + 8.67 continuing scripts; Based on the number of initial and continuing venetoclax scripts among patients in the venetoclax + obinutuzumab arm of the CLL-14 trial (reported in Table 7, p16 of the July 2020 venetoclax PSD).	The number of venetoclax scripts in clinical practice may differ from the clinical trial setting.

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Parameter	Value applied and source	Comment
Obinutuzumab scripts per course	7.355; Based on the number of obinutuzumab scripts among patients in the venetoclax + obinutuzumab arm of the CLL-14 trial (reported in Table 7, p16 of the July 2020 venetoclax PSD).	The number of obinutuzumab scripts in clinical practice may differ from the clinical trial setting.
Venetoclax and obinutuzumab script substitution factor	4.110; Derived by dividing the assumed mean treatment duration for zanubrutinib (70 months) by the total number of venetoclax and obinutuzumab scripts per course (17.025).	The mean treatment duration for zanubrutinib is uncertain and may be longer than estimated. The application of a 5% discount to time to treatment discontinuation may not be reasonable for deriving the estimated financial implications to the PBS. The PBAC considered discounting should not be applied for the financial estimates.
Proportion of zanubrutinib scripts each year	13.53%; Derived by dividing the assumed mean treatment duration for venetoclax by the assumed mean treatment duration for zanubrutinib (9.47 months ÷ 70 months = 13.5%), equating to 7.39 years (1 ÷ 13.5% = 7.39).	The submission's assumption of a zanubrutinib treatment duration of 7.39 years was not adequately justified.

Source: 'Section4_TN CLL' Excel workbook.

Abbreviations: BTK = Bruton's tyrosine kinase, PSCR = pre-sub-committee response, PSD = public summary document

The redacted values correspond to the following ranges:

¹ < 500

6.81 The estimated net cost to the PBS/RPBS of listing zanubrutinib, based on published prices, is presented in Table 15.

Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated zanubrutinib utilisation						
Venetoclax initial scripts	1	1	1	1	1	1
Venetoclax continuing scripts	2	2	2	2	2	2
Obinutuzumab scripts	2	2	2	2	2	2
Total venetoclax/obinutuzumab scripts	9	9	9	9	9	9
Implied incident venetoclax + obinutuzumab patients ^a	1	1	1	1	1	1
Displaced venetoclax and obinutuzumab scripts ^b	2	2	2	2	2	2
Zanubrutinib scripts ^d	2	2	2	2	9	9
Grandfathered patients ^e	1	1	1	1	1	1
Grandfathered patient scripts	2	1	1	1	1	1
Total zanubrutinib scripts	2	2	2	2	9	9
Cost of zanubrutinib to the PBS/RPBS						
PBS/RPBS zanubrutinib cost (\$8,794.57 per script)	3	6	7	8	10	11
Patient copayments (\$17.51/script)	4	4	4	4	4	4
Net cost of zanubrutinib	3	6	7	8	10	11
Net savings from displaced therapies						
Net cost of displaced venetoclax	4	4	4	4	4	4
Net cost of displaced obinutuzumab	4	4	4	4	4	4
Total cost of displaced therapies	4	4	4	4	4	4
Net financial implications of listing zanubrutinib						
Net cost to the PBS/RPBS	5	5	3	6	7	10
Net cost to the MBS	4	4	4	4	4	4
Net cost to the PBS/RPBS/MBS	5	5	3	6	7	10

Source: 'Section4_TN CLL' Excel workbook.

^a Estimated by dividing the total number of dispensed venetoclax and obinutuzumab scripts by the assumed average number of venetoclax and obinutuzumab scripts per patient (17.025).

^b A 40% uptake rate for zanubrutinib was assumed.

^c A substitution rate of 4.110 was assumed. The substitution rate was derived by dividing the estimated duration of zanubrutinib treatment (70 months) by the estimated number of venetoclax and obinutuzumab scripts per patient (1 venetoclax initial + 8.67 venetoclax continuing + 7.355 obinutuzumab = 17.025 scripts per patient).

^d Based on assumed 70 zanubrutinib scripts per patient per treatment course, with 13.5% of zanubrutinib scripts for each treated patient occurs each year (calculated as 9.47 months ÷ 70 months = 13.5%). Assumed an additional 12.18 scripts per patient for < 500 grandfathered patients in Year 1.

^e The submission stated that the sponsor intends to commence a compassionate access program in January 2023, which would result in an estimated < 500 patients requiring grandfathered treatment with zanubrutinib.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$10 million to < \$20 million

⁴ net cost saving

⁵ \$0 to < \$10 million

⁶ \$20 million to < \$30 million

⁷ \$30 million to < \$40 million

⁸ \$40 million to < \$50 million

⁹ 5,000 to < 10,000

¹⁰ \$50 million to < \$60 million

¹¹ \$60 million to < \$70 million

- 6.82 Based on the published prices of venetoclax and obinutuzumab, and the proposed published price of zanubrutinib, the total cost to the PBS/RPBS/MBS of listing zanubrutinib was estimated to be \$0 to < \$10 million in Year 1, increasing to \$50 million to < \$60 million in Year 6, a total cost of \$100 million to < \$200 million over the first 6 years of listing. The additional cost to the PBS/RPBS/MBS was driven by the higher proposed published price of zanubrutinib compared to the cost-minimised price of zanubrutinib (i.e., based on the published prices of venetoclax + obinutuzumab).
- 6.83 The estimated number of zanubrutinib scripts appeared to be underestimated due to the following reasons:
- The available PBS data for venetoclax and obinutuzumab in 2021, which was used to estimate utilisation of zanubrutinib, was immature, and does not represent the full treatment course for some patients (i.e., patients who would have initiated treatment in January 2020 to November 2020 and continued into 2021 had venetoclax + obinutuzumab been listed). The PBAC noted PBS data for 2022 is available to estimate utilisation.
 - Uptake of zanubrutinib may be higher than estimated, given that zanubrutinib is an oral treatment, and given that the PBS restrictions for fixed duration venetoclax do not allow retreatment with venetoclax in the event of disease progression. The PSCR stated that the assumed uptake rate in Years 1 to 6 of listing (40%) was likely to be optimistic. The PBAC considered the uptake of 40% to be potentially reasonable although very uncertain.
 - The submission assumed that zanubrutinib script utilisation for each patient (i.e., based on the mean treatment duration of 70 months) would be evenly spread over 7.39 years, which reduced the utilisation during the initial 6 years of listing. The PSCR stated that this assumption was made for simplicity given the market dynamics.
 - The mean treatment duration for zanubrutinib is uncertain and may be longer than estimated. The PBAC noted removing the discounting (see Table 14) will increase the treatment duration.
 - The availability of an oral therapy for patients with previously untreated CLL/SLL, which may result in growth of the CLL/SLL market. The PBAC considered with zanubrutinib being oral and relatively well tolerated that there is a risk that patients will commence treatment earlier and this risk should be managed with a Risk Sharing Arrangement (RSA).
- 6.84 The submission also claimed that listing of zanubrutinib would be associated with a reduction in tumour lysis syndrome prophylaxis/monitoring costs associated with venetoclax. The submission estimated a cost of \$1,329 per patient, based on the estimated tumour lysis syndrome costs included in the July 2020 venetoclax submission, inflated to 2022 prices. A proportion of the tumour lysis syndrome costs

would be applicable to state health budgets (e.g., costs associated with hospital admission).

Financial Management – Risk Sharing Arrangements

- 6.85 The submission noted that the Department may wish to combine caps on zanubrutinib in the treatment naïve and relapsed/refractory settings to manage expenditure related to sequencing of BTKi/BCL-2i treatments. The submission proposed a combined RSA across the treatment naïve and relapsed refractory settings, and noted that a combined cap may include the following:
- A weighted price for zanubrutinib across the treatment naïve and relapsed/refractory settings, with weightings based on prescription volume of BTK inhibitor/BCL-2i agents in each setting.
 - Utilisation in the relapsed/refractory setting would be combined with utilisation in the treatment naïve setting based on the estimates provided in each financial model, and expenditure calculated based on the weighted price.
 - Any use beyond the proposed annual subsidisation caps would result in the application of a 1% rebate.
- 6.86 The PSCR stated that there is a strong financial rationale for a combined RSA across the treatment naïve and relapsed and refractory CLL/SLL settings to manage uncertainty in uptake and erosion between the settings, and potentially lead to cost savings over the 5-year RSA Deed period. The pre-PBAC response affirmed this as the preferred approach.
- 6.87 The submission acknowledged that, given the changing BTKi/BCL-2i landscape, agents from both BTKi and BCL-2i classes may join the combined RSA in future. If a shared RSA is recommended, the sponsor requested separate PBS item codes in the treatment naïve and relapsed refractory settings to enable utilisation tracking in each line of therapy. However, the basis for this request was unclear.
- 6.88 The ESC noted that if there are separate PBS item codes for the two treatment settings, then separate SPAs could be applied, and a weighted price would not be required. The ESC further noted that, if recommended, it would be appropriate for zanubrutinib to join the current RSA in place for relapsed/refractory CLL/SLL so that the cost per patient in the relapsed/refractory setting for zanubrutinib is equivalent to that for the other therapies. The ESC noted that if zanubrutinib use in the treatment naïve setting was to be included in the current RSA, then the subsidisation caps would need to be increased to account for this use.
- 6.89 The ESC noted an alternative approach would be for a single line agnostic listing for zanubrutinib i.e., a listing for the ‘treatment of CLL/SLL’. In this situation a weighted price for zanubrutinib across the two settings would be required, and the options would be for (i) zanubrutinib to have a separate RSA or (ii) zanubrutinib to join the RSA for in place for relapsed/refractory CLL/SLL. The ESC noted that if zanubrutinib did not

join the current RSA, then the price for zanubrutinib in the relapsed/refractory setting should be based on the cost per patient that was considered cost-effective for ibrutinib at the time of its listing. For this scenario the ESC requested estimates of the weights for calculating a single price for use across both settings be provided in the pre-PBAC response.

- 6.90 The pre-PBAC response suggested that these weights should be based on the estimated use of zanubrutinib in the treatment naïve setting compared to the estimated use for the entire BTKi therapies in the relapsed/refractory setting. The weightings provided in the pre-PBAC response could not be replicated.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC recommended extending the listing of zanubrutinib to include treatment naïve chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL). The PBAC considered the nominated comparator of venetoclax plus obinutuzumab was appropriate. The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of zanubrutinib would be acceptable if it were cost-minimised to venetoclax plus obinutuzumab. The PBAC considered a risk sharing arrangement (RSA) would be required to manage the risks of the duration of treatment with zanubrutinib being longer than modelled and earlier use in patients not meeting the iwCLL criteria for initiating treatment.
- 7.2 The PBAC noted the input from individuals, health professionals and organisations regarding the benefits of treatment with zanubrutinib including ease of taking zanubrutinib, efficacy, high tolerability, the potential for reduced hospital visits, and the opportunity for improved quality of life through the ability to return to work and participate in the community. The PBAC considered that it would be ideal to have a range of first-line subsidised treatment options available to patients, with treatment able to be tailored to the needs of an individual patient. Factors considered could include co-existing disease, the extent of lymph node involvement, the goals of treatment, a preference for fixed duration or continuous treatment, and the acceptability of an initial period of intravenous treatment.
- 7.3 The PBAC noted consumer comments detailing the difficulty of the 'watch and wait' approach for asymptomatic patients, which puts pressure on clinicians to initiate treatment. The PBAC considered that the availability of an oral treatment could lead to inappropriate use earlier than indicated. To reduce the potential for inappropriate use, the PBAC considered that it would be appropriate to include the International Workshop on CLL (iwCLL) criteria for commencing treatment (latest version, which was Hallek et al, 2018 at the time of the PBAC consideration) in the restriction for zanubrutinib, and to flow this change onto the restrictions for all treatments for CLL/SLL patients with both treatment naïve and relapsed/refractory disease.

- 7.4 The PBAC noted that the restrictions for venetoclax plus obinutuzumab in first-line CLL/SLL require patients to be inappropriate for fludarabine-based chemoimmunotherapy and have a cumulative illness rating scale (CIRS) score > 6 (excluding CLL-induced illness or organ damage) or creatinine clearance < 70 mL/min. However, the PBAC recalled that at the December 2022 intracycle meeting it had considered it was no longer clinically relevant to include the CIRS score in restrictions for CLL/SLL therapies given the score was developed to assess the ability of a patient to tolerate chemoimmunotherapy and was less relevant for targeted agents. The PBAC recalled its previous consideration that, rather than relying on the CIRS score and/or creatinine clearance < 70 mL/min, it would be more clinically appropriate for clinicians/patients to decide the most appropriate treatment regimen for a particular patient, which may involve consideration of a broader range of factors including biological characteristics of the disease and an individual's specific organ sensitivities (e.g., cardiac or renal risk).
- 7.5 The PBAC similarly advised the restriction criteria relating to 'inappropriate for fludarabine-based chemoimmunotherapy', having CIRS > 6, or having creatinine clearance < 70 mL/min should not be included in the zanubrutinib restriction.
- 7.6 The concurrent submission for zanubrutinib monotherapy for the treatment of relapsed/refractory CLL/SLL was also recommended at the March 2023 PBAC meeting. The PBAC considered that it would be appropriate for zanubrutinib to have separate restrictions in the treatment naïve and in the relapsed/refractory settings and to align the restrictions with the existing CLL/SLL restrictions. The PBAC noted advice from the Department that separate PBS item codes for treatment naïve disease and relapsed/refractory disease would allow easier administration of any RSA caps.
- 7.7 The PBAC considered that the nominated main comparator of venetoclax plus obinutuzumab was appropriate. The PBAC noted that acalabrutinib, and acalabrutinib plus obinutuzumab, were appropriately nominated as near market comparators, however had not been recommended for listing.
- 7.8 The PBAC noted that the clinical evidence consisted of open label trials with blinded assessments, that patient populations across the SEQUOIA trial for zanubrutinib and the CLL-14 trial for venetoclax plus obinutuzumab were broadly similar, and that the duration of follow-up for the trials differed. The PBAC noted the treatment regimens also differed with venetoclax plus obinutuzumab being administered for a fixed duration (maximum of 12 months) and zanubrutinib being administered until progression.
- 7.9 The PBAC noted that the comparative efficacy and safety of zanubrutinib versus venetoclax plus obinutuzumab was based on indirect treatment comparisons of zanubrutinib from the SEQUOIA trial to venetoclax plus obinutuzumab from the CLL-14 trial. The PBAC noted that progression free survival and overall survival for zanubrutinib and venetoclax plus obinutuzumab were broadly similar. The PBAC noted that based on a median follow-up of just over 2 years for the SEQUOIA trial that a

difference in overall survival would not be expected given the good prognosis for treatment naïve CLL/SLL patients.

- 7.10 The PBAC noted that three unanchored MAIC models were developed for zanubrutinib versus venetoclax + obinutuzumab with results for zanubrutinib based on pooled data from patients in the SEQUOIA trial with del17p and non del17p, and that none of the models demonstrated a statistically significant difference in PFS or OS. The PBAC considered that the treatment effect modifiers flagged for matching were appropriate. The PBAC noted that the submission presented Model 1 to support the clinical claim, and although a justification was not provided for the selection of this model over the other two, the results across the three models were reasonably consistent.
- 7.11 The PBAC noted that unanchored unadjusted indirect treatment comparisons were presented for safety outcomes, and that patients treated with venetoclax plus obinutuzumab experienced numerically higher rates of neutropenia, anaemia, thrombocytopenia and diarrhoea, and that the discontinuation rate for patients treated with zanubrutinib was approximately half that for patients treated with venetoclax plus obinutuzumab, although the difference may reduce over time given the longer treatment duration with zanubrutinib.
- 7.12 The PBAC considered that the clinical claims of non-inferior effectiveness and safety for zanubrutinib versus venetoclax plus obinutuzumab were reasonably supported by the data, but with some uncertainty given the indirect treatment comparisons presented and the immaturity of the clinical evidence particularly for overall survival.
- 7.13 The PBAC noted that the submission had presented a CMA of zanubrutinib compared with venetoclax plus obinutuzumab to derive a price for zanubrutinib that resulted in the same cost per course per patient as venetoclax plus obinutuzumab. The PBAC noted that the CMA was conducted over a period of 10 years, and that a 5% discount rate was applied to the time to treatment discontinuation curve for zanubrutinib. The PBAC considered that the submission's approach to the CMA (Table 11) was reasonable with adjustments described below, and that a time frame of 10 years was appropriate in the context of first-line treatment of CLL/SLL.
- 7.14 The PBAC noted that the analysis included in the submission capped the time to treatment discontinuation for zanubrutinib using progression-free survival data for the venetoclax + obinutuzumab arm of the CLL-14 trial and that introduced uncertainty. The PBAC noted that the survival capping was removed in the analysis presented in the pre-PBAC response and considered that this was appropriate. The PBAC noted that the revised equi-effective doses were:
- One initial and 8.67 continuing venetoclax scripts plus 7.355 obinutuzumab scripts are equivalent to 70.73 months of zanubrutinib treatment at a dose of 304 mg daily (68.09 zanubrutinib scripts).
- 7.15 The PBAC noted that the sponsor in their pre-PBAC response had proposed to reduce

the cost offsets for zanubrutinib in the model by 50% to better reflect real-world offsets compared to offsets in the clinical trials. The PBAC considered that this was appropriate.

- 7.16 The PBAC noted that the submission used a market share approach to derive the expected utilisation and the cost to the PBS/RPBS over 6 years and considered that this was appropriate, although noted it would be more appropriate to define the market using more recent PBS data for venetoclax and obinutuzumab. The PBAC noted the financial estimates assumed that zanubrutinib would be used in 40% of patients who would otherwise have initiated treatment on venetoclax plus obinutuzumab, that approximately < 500 patients would be grandfathered from the sponsor's compassionate access program, and that zanubrutinib would not grow the market. The PBAC considered that the submission's assumption that zanubrutinib would be used instead of venetoclax plus obinutuzumab in 40% of patients initiating therapy each year to be potentially reasonable although very uncertain. The PBAC considered the grandfathered patients would already be accounted for given the prevalence approach used and should not be accounted for separately. The PBAC noted discounting was applied to the treatment duration but, consistent with standard practice for estimating the financial impact, this should be removed from the calculations.
- 7.17 The PBAC noted that overall due to the cost for zanubrutinib accruing over a longer period of time than the cost-offsets for venetoclax plus obinutuzumab that in the initial years there would be a cost saving however this would reverse to a net cost in later years. The PBAC noted there would also be a net cost with the listing of zanubrutinib over the longer term due to the inclusion of cost offsets in the CMA and due to discounting being included in the CMA but not in the calculation for the financial estimates.
- 7.18 The PBAC noted that in the pre-PBAC response it was estimated that patient numbers, and therefore script numbers would increase by approximately 30% due to the removal of the requirement for patients to be 'inappropriate for fludarabine-based chemoimmunotherapy'. However, the PBAC considered that the use of fludarabine-based chemoimmunotherapy in CLL is low and declining and as such, there would be no increase in use associated with the restriction change.
- 7.19 The PBAC noted that the sponsor had proposed a RSA, and considered that this was appropriate to manage the risk of (i) the treatment duration being longer than modelled with the additional use potentially not being cost-effective and (ii) earlier use in patients not meeting the iwCLL criteria for initiating treatment with such use potentially not being cost-effective. The PBAC noted that while venetoclax has a RSA in the first-line setting, given it is a fixed duration, the identified risks regarding zanubrutinib use do not apply and hence it may not be appropriate to add zanubrutinib to the existing RSA for venetoclax.

- 7.20 The PBAC recommended that the restriction should allow for the transition of the approximately < 500 patients who commenced on non-PBS-subsidised zanubrutinib through a compassionate access program to access zanubrutinib on the PBS, provided the patients had met the PBS initiation criteria at time of initiation with non-PBS therapy, and provided that the condition had not progressed whilst the patient was actively being treated with non-PBS-subsidised zanubrutinib.
- 7.21 The PBAC noted that flow-on restriction changes would be required for other therapies for CLL/SLL to ensure the therapies are only prescribed in accordance with the iwCLL guidance (latest version) in relation to when to prescribe drug treatment for this condition/when to monitor the patient without therapy.
- 7.22 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because zanubrutinib is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over venetoclax plus obinutuzumab, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 7.23 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add indication as follows:

Category / Program: GENERAL – General Schedule (Code GE)					
MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ZANUBRUTINIB					
zanubrutinib 80 mg capsule, 120	NEW 1 MP	1	120	5	Brukinsa
Safety Net Rule Penalty Applies? Yes					
Restriction Summary / Treatment of Concept: Authority Required					
Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)					
Treatment Phase: First line drug treatment of this indication					
Clinical criteria:					
The condition must be untreated with drug treatment at the time of the first dose of this drug; or					
Patient must have developed an intolerance of a severity necessitating permanent treatment withdrawal following use of another drug PBS-indicated as first-line drug treatment of CLL/SLL					

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	AND
	Clinical criteria:
	The treatment must only be prescribed for patients with active disease in accordance with the International Workshop on CLL (iwCLL) guidance (latest version) in relation to when to prescribe drug treatment for this condition
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this PBS indication.
	Treatment criteria:
	Patient must be undergoing initial treatment with this drug – this is the first prescription for this drug; or
	Patient must be undergoing continuing treatment with this drug – the condition has not progressed whilst the patient has actively been on this drug
	Administrative advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Administrative advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative advice: No increase in the maximum number of repeats may be authorised.
	Administrative advice: Special Pricing Arrangements apply.
	Administrative advice: The latest International Workshop on CLL (iwCLL) provides guidance on various aspects of management of CLL/SLL. Notably, two of these are: (1) when to treat versus when to monitor the patient without therapy – see 'Indications for treatment' section; and (2) recognising progressive disease – see 'Definition of response, relapse, and refractory disease' section. See the following literature reference for details: Hallek, M et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. <i>Blood</i> vol. 131, 25 (2018): 2745-2760.

Flow-on changes

8.2 Amend the following venetoclax listings as follows:

Category / Program: GENERAL – General Schedule (Code GE)							
MEDICINAL PRODUCT	PBS item code	Max. packs	qty	Max. units	Qty	No. of Rpts	Available brands
VENETOCLAX							
venetoclax 10 mg tablet [14] (&)	12188L MP	1		1		0	Venclexta
venetoclax 50 mg tablet [7] (&)							
venetoclax 100 mg tablet [7] (&)							
venetoclax 100 mg tablet [14], 1 pack							
							Safety Net Rule Penalty Applies? No
Amend Restriction Summary / Treatment of Concept: Authority Required							
Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)							

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	Treatment Phase: Initial treatment in first-line therapy - Dose titration (weeks 1 to 4 of a 5-week ramp-up schedule)
	Clinical criteria:
	The condition must be untreated
	<i>The condition must be untreated with drug treatment at the time of the first dose of this drug; or</i>
	<i>Patient must have developed an intolerance of a severity necessitating permanent treatment withdrawal following use of another drug PBS-indicated as first line drug treatment of CLL/SLL</i>
	AND
	Clinical criteria:
	Patient must be inappropriate for fludarabine based chemo-immunotherapy
	AND
	Clinical criteria:
	<i>The treatment must only be prescribed for patients with active disease in accordance with the International Workshop on CLL (iwCLL) guidance (latest version) in relation to when to prescribe drug treatment for this condition</i>
	AND
	Clinical criteria:
	The treatment must be in combination with obinutuzumab (refer to Product Information for timing of obinutuzumab and venetoclax doses)
	AND
	Clinical criteria:
	Patient must have a creatinine clearance 30 mL/min or greater
	AND
	Clinical criteria:
	Patient must have a total cumulative illness rating scale (CIRS) score of greater than 6 (excluding CLL-induced illness or organ damage); or
	Patient must have a creatinine clearance less than 70 mL/min
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Administrative advice: <i>The latest International Workshop on CLL (iwCLL) provides guidance on various aspects of management of CLL/SLL. Notably, two of these are:</i> <i>(1) when to treat versus when to monitor the patient without therapy – see ‘Indications for treatment’ section; and</i> <i>(2) recognising progressive disease – see ‘Definition of response, relapse, and refractory disease’ section.</i> <i>See the following literature reference for details:</i> <i>Hallek, M et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood vol. 131, 25 (2018): 2745-2760.</i>

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Category / Program: GENERAL – General Schedule (Code GE)							
MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. packs	qty	Max. units	Qty	No. of Rpts	Available brands
VENETOCLAX							
venetoclax 100 mg tablet, 120	12205J MP	1		120		4	Venclexta
Safety Net Rule Penalty Applies? Yes							
Restriction Summary / Treatment of Concept: Authority Required *****UNCHANGED*****							
	Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)						
	Treatment Phase: First continuing treatment (treatment cycles 2 to 6 inclusive) of first-line therapy						
	Clinical criteria:						
	Patient must have previously received PBS-subsidised treatment with this drug for this condition						
	AND						
	Clinical criteria:						
	The treatment must be in combination with obinutuzumab (refer to Product Information for timing of obinutuzumab and venetoclax doses)						
	AND						
	Clinical criteria:						
	The treatment must cease upon disease progression						
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.						
	Administrative Advice: No increase in the maximum number of repeats may be authorised.						
	Administrative Advice: Special Pricing Arrangements apply.						
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.						

Category / Program: GENERAL – General Schedule (Code GE)							
MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. packs	qty	Max. units	Qty	No. of Rpts	Available brands
VENETOCLAX							
venetoclax 100 mg tablet, 120	12199C MP	1		120		5	Venclexta
Safety Net Rule Penalty Applies? Yes							
Restriction Summary / Treatment of Concept: Authority Required *****UNCHANGED*****							
	Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)						
	Treatment Phase: Second and final continuing treatment prescription (treatment cycles 7 to 12 inclusive) of first-line therapy						
	Clinical criteria:						
	Patient must have previously received PBS-subsidised treatment with this drug for this condition						

AND
Clinical criteria:
The treatment must cease upon disease progression; or
The treatment must cease upon completion of 12 cycles of treatment with this drug for this condition, whichever comes first
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.

Category / Program: GENERAL – General Schedule (Code GE)							
MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. packs	qty	Max. units	qty	No.of Rpts	Available brands
VENETOCLAX							
venetoclax 10 mg tablet, 2	12999E MP	7		14		0	Venclexta
venetoclax 50 mg tablet, 7	11648C MP	1		7		0	Venclexta
Safety Net Rule Penalty Applies? No							
Restriction Summary / Treatment of Concept: Authority Required *****UNCHANGED*****							
Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)							
Treatment Phase: Dose modification							
Clinical criteria:							
The treatment must be for dose titration purposes							
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.							
Administrative Advice: No increase in the maximum number of repeats may be authorised.							
Administrative Advice: Special Pricing Arrangements apply.							
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.							

The restriction and flow-on changes may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the

merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.