7.04 IBRUTINIB, Capsule 140 mg, Tablet 280 mg, Tablet 420 mg, Imbruvica®, JANSSEN-CILAG PTY LTD.

1 Purpose of submission

1.1 The standard re-entry resubmission requested a General Schedule Authority Required listing of ibrutinib, for use in combination with venetoclax (IBR+VEN), for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL).

1.2 Listing was requested on the basis of a cost-minimisation approach versus venetoclax + obinutuzumab (VEN+OBI).

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

Component	Description
Population	Patients with previously untreated CLL/SLL ~~who would otherwise be considered fit for treatment with fludarabine based chemoimmunotherapy~~.
Intervention	Fixed duration ibrutinib + venetoclax per the following regimen: • Ibrutinib: 420 mg administered orally once daily as a single-agent lead-in for 3 cycles (where each cycle is 28 days), then continued in combination with venetoclax for a further 12 cycles. • Venetoclax: administered orally once daily starting with a 5-week dose ramp-up (20 mg for 1 week followed by 1 week at each dose level of 50 mg, 100 mg, 200 mg), and then continued at the recommended daily dose of 400 mg; added to ongoing ibrutinib therapy commencing in Cycle 4 and continued for a total of 12 cycles.
Comparator	• Fixed duration venetoclax + obinutuzumab (main comparator) • Treat-to-progression zanubrutinib (supplementary comparator) • ~~Fixed duration fludarabine + cyclophosphamide + rituximab~~
Outcomes	Progression free survival, overall survival, overall response rate, complete response rate, MRD negativity, adverse events.
Clinical claim	• In patients with previously untreated CLL/SLL, fixed duration ibrutinib + venetoclax is non-inferior in terms of efficacy and safety compared to fixed duration venetoclax + obinutuzumab. • In patients with previously untreated CLL/SLL, fixed duration ibrutinib + venetoclax is non-inferior in efficacy and safety compared to treat-to-progression zanubrutinib (as a proxy for all available treat-to-progression BTK inhibitor treatments). • ~~Ibrutinib + venetoclax is superior to FCR in terms of efficacy and at least non-inferior in terms of safety, with a different safety profile compared to FCR, and a reduced risk of developing secondary primary malignancies.~~

Source: Table 1.1 of the resubmission; Table 1, p1 of the ibrutinib Public Summary Document, December 2022 intracycle PBAC meeting.
Abbreviations: BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukaemia; FCR, fludarabine + cyclophosphamide + rituximab; MRD, minimal residual disease; SLL, small lymphocytic lymphoma.
Changes compared to submission considered at the December 2022 intracycle PBAC meeting indicated by shaded text (additions) and strikethrough (removals).

2 Background

Registration status

2.1 Ibrutinib was registered on the ARTG for use in combination with venetoclax on 28 March 2023, based on the following indication:

- Ibrutinib as a single agent or in combination with rituximab or obinutuzumab or venetoclax for the treatment of adult patients with previously untreated CLL/SLL.

Previous PBAC consideration

2.2 A submission for ibrutinib, for use in combination with venetoclax, for the treatment of patients with previously untreated CLL/SLL, was submitted for the November 2022 PBAC meeting. The submission was considered and not recommended for listing at the December 2022 intracycle PBAC meeting. A summary of the key matters of concern are presented in Table 2. Paragraph numbers in the Table refer to the ibrutinib Public Summary Document from that meeting. The ESC considered the resubmission had addressed the key matters of concern raised at the December 2022 intracycle PBAC meeting.

Table 2: Summary of key matters of concern

Matter of concern	How the resubmission addresses it
Proposed restriction	
The PBAC noted that, while the existing PBS restriction criteria define the patient populations based on patient suitability for fludarabine-based chemoimmunotherapy, the advice from the clinical consultation was that these criteria are no longer relevant to clinical practice (para 7.1). The PBAC considered that it was no longer clinically relevant to include the CIRS score in restrictions for first-line CLL/SLL therapies, and 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 (para 7.3).	The proposed restriction was broadened to include all patients with previously untreated CLL/SLL.
Main comparator	
The PBAC considered the nominated comparator of fludarabine + cyclophosphamide + rituximab (FCR), although of historical relevance, is no longer the therapy most likely to be replaced in clinical practice given its limited use (para 7.1). The PBAC considered that, should venetoclax + obinutuzumab be listed for all patients regardless of suitability for fludarabine-based chemoimmunotherapy and regardless of CIRS score, there may be a degree of overlap with the likely patient population for ibrutinib + venetoclax, and that a cost comparison would be informative (para 7.10).	The resubmission nominated fixed duration treatment with venetoclax + obinutuzumab as the main comparator. Treat-to-progression zanubrutinib was nominated as a supplementary comparator.
Clinical evidence	

Matter of concern	How the resubmission addresses it
The PBAC considered there was limited clinical evidence presented for ibrutinib + venetoclax. The PBAC noted further follow-up data from the CAPTIVATE study and/or information from the GLOW trial would potentially be informative (para 7.10).	The resubmission presented updated data from the CAPTIVATE study corresponding to a median follow-up of 55.7 months (previously a median follow-up of 38.7 months). The resubmission included results for the GLOW trial, which compared ibrutinib + venetoclax with chlorambucil + obinutuzumab in patients with previously untreated CLL/SLL who are older or have comorbidities. Results corresponding to a median follow-up of 52.1 months were presented.
The PBAC considered the comparison of ibrutinib + venetoclax versus FCR presented in the submission was not an informative basis for the listing of ibrutinib + venetoclax (para 7.1).	Venetoclax + obinutuzumab was nominated as the main comparator in the resubmission. The claim of non-inferior efficacy versus venetoclax + obinutuzumab was based on the results of a Bucher method indirect comparison and an unanchored MAIC of efficacy outcomes for ibrutinib + venetoclax (GLOW) versus venetoclax + obinutuzumab (CLL-14). The claim of non-inferior safety versus venetoclax + obinutuzumab was based on an unanchored unadjusted (naïve) indirect treatment comparison of safety outcomes for ibrutinib + venetoclax (GLOW) and venetoclax + obinutuzumab (CLL-14).
The PBAC considered the benefit of ibrutinib + venetoclax (fixed duration) versus internationally accepted current standard treatments such as BTK inhibitor monotherapy (treat to progression) is unclear (para 7.5).	Zanubrutinib (treat-to-progression) was nominated as a supplementary comparator.
The PBAC considered that the outcome of subsequent treatment with BTK inhibitors or venetoclax was unclear, noting that only nine patients in the CAPTIVATE study were retreated with single agent ibrutinib following disease progression (para 7.5).	The resubmission included additional data on outcomes for patients in the CAPTIVATE and GLOW trials who received retreatment with ibrutinib after experiencing disease progression.
The PBAC noted that cardiac adverse events including atrial fibrillation and cardiac failure, and haemorrhagic events were reported with ibrutinib + venetoclax. The PBAC also noted that the TGA Delegate's Overview stated, 'there is an increasing strength in the signal for cardiovascular risk for ibrutinib, a known risk with this medicine' (para 7.6).	The resubmission presented the latest Periodic Benefit Risk Evaluation Report for ibrutinib as well as the results of an updated literature search for publications reporting on adverse events associated with ibrutinib.
Economic analysis	
The PBAC considered that the cost-effectiveness of ibrutinib + venetoclax was unable to be reliably assessed due to the uncertain magnitude of benefit, which relied on immature data from the CAPTIVATE study, and an unanchored, unadjusted indirect comparison versus FCR (para 7.7).	The nominated main comparator in the resubmission was venetoclax + obinutuzumab. The clinical claim of noninferior efficacy underpinning the cost-minimisation was based on the results of a Bucher method indirect comparison and an unanchored MAIC of ibrutinib + venetoclax (GLOW) versus venetoclax + obinutuzumab (CLL-14). The clinical claim of non-inferior safety was based on an unanchored unadjusted (naïve) indirect treatment comparison of ibrutinib + venetoclax (GLOW) and venetoclax + obinutuzumab (CLL-14).
The PBAC considered a cost comparison of ibrutinib + venetoclax and venetoclax + obinutuzumab would be informative in any resubmission (para 7.10).	The resubmission presented a cost-minimisation approach comparing treatment with fixed duration ibrutinib + venetoclax to fixed duration venetoclax + obinutuzumab. The cost-minimisation was based on the fixed duration treatment regimens included in the clinical trials (ibrutinib + venetoclax administered over a total of 15 cycles; and venetoclax + obinutuzumab administered over a total of 12 cycles).
Financial issues	

Matter of concern	How the resubmission addresses it
The PBAC noted the proposed restrictions and comparator in any resubmission will inform the approach for the economic model and financial forecasts (para 7.10).	The price of ibrutinib was derived based on the results of a cost-minimisation approach of ibrutinib + venetoclax versus venetoclax + obinutuzumab. The financial impacts were estimated using a market share approach, assuming that ibrutinib + venetoclax will substitute for venetoclax + obinutuzumab.

Source: Ibrutinib Public Summary Document (PSD), December 2022 intracycle PBAC meeting – paragraph (para) numbers refer to the relevant paragraph from the Ibrutinib PSD.
Abbreviations: BTK inhibitor; CIRS, Cumulative Illness Rating Scale; CLL, chronic lymphocytic leukaemia; FCR, fludarabine + cyclophosphamide + rituximab; MAIC, matching adjusted indirect comparison; SLL, small lymphocytic lymphoma; TGA, Therapeutic Goods Administration.

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

3 Requested listing

3.1 An abbreviated version of the requested listing is presented below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. qty packs	Max. qty units	№.of Rpts	Dispensed Price for Max. Qty	Available brands
Initial treatment in first-line therapy (3-cycle lead-in)					
ibrutinib 140 mg capsule, 90	1	90	2	$7,953.68 (published) $[redacted] (effective) [a]	Imbruvica
ibrutinib 280 mg tablet, 30	1	30	2	$5,356.49 (published) $[redacted] (effective) [a]	Imbruvica
ibrutinib 420 mg tablet, 30	1	30	2	$7,953.68 (published) $[redacted] (effective) [a]	Imbruvica
First continuing treatment (treatment cycles 4-9) in first-line therapy					
ibrutinib 140 mg capsule, 90	1	90	5	$7,953.68 (published) $[redacted] (effective) [a]	Imbruvica
ibrutinib 280 mg tablet, 30	1	30	5	$5,356.49 (published) $[redacted] (effective) [a]	Imbruvica
ibrutinib 420 mg tablet, 30	1	30	5	$7,953.68 (published) $[redacted] (effective) [a]	Imbruvica
Grandfather treatment - Transitioning from non-PBS to PBS-subsidised supply of first-line therapy					
ibrutinib 140 mg capsule, 90	1	90	5	$7,953.68 (published) $[redacted] (effective) [a]	Imbruvica
ibrutinib 280 mg tablet, 30	1	30	5	$5,356.49 (published) $[redacted] (effective) [a]	Imbruvica
ibrutinib 420 mg tablet, 30	1	30	5	$7,953.68 (published) $[redacted] (effective) [a]	Imbruvica
Second continuing treatment (treatment cycles 10-15) in first-line therapy					
ibrutinib 140 mg capsule, 90	1	90	4	$7,953.68 (published) $[redacted] (effective) [a]	Imbruvica
ibrutinib 280 mg tablet, 30	1	30	4	$5,356.49 (published) $[redacted] (effective) [a]	Imbruvica
ibrutinib 420 mg tablet, 30	1	30	4	$7,953.68 (published) $[redacted] (effective) [a]	Imbruvica

Category / Program: General Schedule
Prescriber type: ☒Medical Practitioners

Restriction type: ☒ Authority Required (telephone/online via PBS Authorities system)
~~Condition:~~ ~~Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)~~
Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Treatment Phase: Initial treatment in first-line therapy (treatment cycles 1 to 3 inclusive)
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,
AND
Clinical criteria:
The treatment must only be prescribed for a patient 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 in combination with venetoclax (refer to Product Information for timing of ibrutinib and venetoclax doses).
Prescriber Instruction:
There are more ibrutinib capsules (or tablets) in a pack than is required for the completion of a treatment cycle. The patient must not discard any remaining capsules (or tablets) after the completion of any treatment cycle as these capsules (or tablets) will be required for the doses in the final treatment cycle (i.e. treatment cycle 15).
Category / Program: General Schedule
Prescriber type: ☒Medical Practitioners
Restriction type: ☒ Authority Required (telephone/online via PBS Authorities system)
~~Condition:~~ ~~Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)~~
Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Treatment phase: First continuing treatment (treatment cycles 4-9) 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 venetoclax (refer to Product Information for timing of ibrutinib and venetoclax doses)
AND
Clinical criteria:
The treatment must cease upon disease progression.
Prescriber Instruction:
There are more ibrutinib capsules (or tablets) in a pack than is required for the completion of a treatment cycle. The patient must not discard any remaining capsules (or tablets) after the completion of any treatment cycle as these capsules (or tablets) will be required for the doses in the final treatment cycle (i.e. treatment cycle 15).
Category / Program: General Schedule
Prescriber type: ☒Medical Practitioners
Restriction type: ☒ Authority Required (telephone/online PBS Authorities system)
~~Condition:~~ ~~Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)~~
Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Treatment phase: Grandfather treatment - Transitioning from non-PBS to PBS-subsidised supply *of first-line therapy*
Clinical criteria:

Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to [PBS listing date XXX].
AND
Clinical criteria:
Patient must not have developed disease progression while receiving treatment with this drug for this condition.
AND
Clinical criteria:
The condition must *have been* ~~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 *at the time of receiving non-PBS-subsidised treatment with this drug for this condition*,
AND
Clinical criteria:
The treatment must only be prescribed for a patient 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 in combination with venetoclax (refer to Product Information for timing of ibrutinib and venetoclax doses).
Prescriber instruction: *A patient may qualify for PBS-subsidised treatment under this restriction once only.*
Prescriber instruction: *For continuing PBS-subsidised treatment, a 'Grandfathered" patient must qualify under the 'Continuing treatment' First continuing treatment (treatment cycles 4 to 9 inclusive) of first-line therapy criteria.*
Prescriber Instruction: There are more ibrutinib capsules (or tablets) in a pack than is required for the completion of a treatment cycle. The patient must not discard any remaining capsules (or tablets) after the completion of any treatment cycle as these capsules (or tablets) will be required for the doses in the final treatment cycle (i.e. treatment cycle 15).
Category / Program: General Schedule
Prescriber type: ☒Medical Practitioners
Restriction type: ☒ Authority Required (telephone/online via PBS Authorities system)
~~**Condition:** Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)~~
Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Treatment phase: Second and final continuing treatment (treatment cycles 10 to 15 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 venetoclax (refer to Product Information for timing of ibrutinib and venetoclax doses)
AND
Clinical criteria:
The treatment must cease upon disease progression, OR
The treatment must cease upon completion of 15 cycles of *PBS-subsidised* treatment with this drug for this condition, whichever comes first.
Prescriber Instruction:
There are more ibrutinib capsules (or tablets) in a pack than is required for the completion of a treatment cycle. The patient must not discard any remaining capsules (or tablets) after the completion of any treatment cycle as these capsules (or tablets) will be required for the doses in the final treatment cycle (i.e. treatment cycle 15).

[a] Estimated effective price only. The effective price for ibrutinib is to be calculated based on the cost-minimisation of ibrutinib + venetoclax to venetoclax + obinutuzumab using the effective price of venetoclax in previously untreated CLL/SLL.

3.2 The resubmission proposed a special pricing arrangement, with an effective price for ibrutinib to be determined based on the CMA of ibrutinib + venetoclax versus venetoclax + obinutuzumab using the effective price of venetoclax in previously untreated CLL/SLL.

3.3 In addition to the 140 mg ibrutinib capsules, which are currently PBS listed for use in relapsed/refractory CLL/SLL, the resubmission also proposed listing of ibrutinib 420 mg and 280 mg tablets. A minor submission requesting listing of ibrutinib 140 mg, 280 mg, 420 mg and 560 mg tablets under the same conditions as PBS-listed ibrutinib 140 mg capsules received a positive recommendation at the November 2020 PBAC meeting. However, ibrutinib tablets were not available on the PBS at the time of the evaluation. While the 420 mg tablets will reduce pill burden for patients on a 420 mg dose, patients who require a dose reduction will need to obtain a supply of the 140 mg capsules or 280 mg tablets.

3.4 The proposed listing is narrower than the TGA indication, which includes treatment of adult patients with previously untreated CLL/SLL as a single agent, or in combination with rituximab, obinutuzumab, or venetoclax.

3.5 The proposed clinical criteria are consistent with the updated clinical criteria included in the venetoclax and zanubrutinib PBS listings. The creatinine clearance, Cumulative Illness Rating Scale (CIRS) score and WHO performance status criteria included in the November 2022 submission have been removed in the resubmission. The resubmission presented data from the CAPTIVATE study (patients aged 18-70 years with an ECOG performance status of 0-2) and the GLOW trial (patients aged ≥65 years; or 18-65 years with a CIRS score >6 or creatinine clearance <70 mL/min) to support the broader requested listing.

3.6 The resubmission stated that across the three treatment phases, the total number of ibrutinib bottles/packs dispensed (initial + repeats) will provide the precise number of ibrutinib capsules (or tablets) required to cover exactly 15 cycles of fixed dose IBR+VEN. The sponsor requested the following Prescriber Instruction be included in the Initial treatment and First continuing treatment restrictions: There are more ibrutinib capsules (or tablets) in a pack than is required for the completion of a treatment cycle. The patient must not discard any remaining capsules (or tablets) after the completion of any treatment cycle as these capsules (or tablets) will be required for the doses in the final treatment cycle (i.e. treatment cycle 15).

3.7 The resubmission requested a grandfather restriction for patients who initiate treatment with ibrutinib + venetoclax via an early access program, which is anticipated to start approximately 3 months prior to PBS listing. The sponsor stated that approximately 24 patients are expected to be grandfathered onto the PBS.

3.8 New initial and continuing restrictions for venetoclax, to allow treatment in combination with ibrutinib, were also proposed in the resubmission. The ESC noted that the sponsor of venetoclax would need to agree to the proposed restrictions.

3.9 The resubmission noted that a grandfather restriction may be required for venetoclax, should the early access program be open longer than 3 months (beyond the 3-cycle lead-in of ibrutinib as part of the ibrutinib + venetoclax treatment regimen). A grandfather restriction for venetoclax was not presented in the resubmission.

3.10 The sponsor requested that the ibrutinib relapsed/refractory PBS restriction be updated to allow subsequent retreatment with ibrutinib for patients treated with fixed duration ibrutinib + venetoclax. The resubmission proposed the following change to the treatment criterion included in the ibrutinib relapsed/refractory PBS restriction ('Patient must not be undergoing retreatment with this drug where prior, active treatment of CLL/SLL with this same drug was unable to prevent disease progression'): 'Patient must not be undergoing retreatment with any drug where prior, active treatment of CLL/SLL with this same drug was unable to prevent disease progression while on treatment (i.e., without a treatment-free interval)'. A specific progression-free interval after completion of ibrutinib + venetoclax treatment was not proposed in the resubmission. The Pre-Sub-Committee Response (PSCR) stated that "the ESC has previously highlighted that "it may be reasonable to allow re-treatment, particularly if it is preceded by a gap of 12 or 24 months post first-line treatment" and thus [the sponsor] is requesting retreatment is allowed with ibrutinib monotherapy (or venetoclax) after I+V if a patient's CLL progressed while off treatment." The PSCR also highlighted that "in May 2023, NICE recommended I+V for previously untreated CLL, and allowed retreatment with these treatments on the NHS, as UK clinical experts informed NICE that patients would still respond to these therapies in the relapsed disease ("FD I+V reduces the chances of CLL becoming resistant to them, unlike what might happen for 'treat to progression' monotherapies like ibrutinib and acalabrutinib")." The ESC considered the evidence for retreatment with ibrutinib is immature, and noted that patients would have the option of treatment with other BTK inhibitor therapies that are available in the relapsed/refractory setting. The pre-PBAC Response maintained that the sponsor considers it appropriate to allow retreatment with ibrutinib to "provide additional prescribing flexibility and clinical autonomy."

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

4 Population and disease

4.1 CLL is characterised by the progressive accumulation of functionally incompetent B-lymphocytes in the blood, bone marrow, lymph nodes, spleen and liver. Typical symptoms associated with CLL include swollen lymph nodes, pain, anaemia, infections, increased or unexplained bleeding/bruising, excessive nocturnal sweating and unintentional weight loss. In Australia, CLL is more common in men than women (62% versus 38%), with a mean age at diagnosis in 2019 of 71.1 years (males

70.7 years, females 71.7 years). The five-year relative survival rate in Australia in 2015-2019 was 86.0% (AIHW, 2023).

4.2 SLL, another type of B-cell malignancy, is recognised as the same pathological entity as CLL, with a different clinical presentation. In CLL, abnormal lymphocytes are predominantly found in blood, bone marrow and lymphoid tissue (peripheral blood involvement), whereas in SLL, abnormal lymphocytes are predominantly located in lymph nodes, bone marrow and other lymphoid tissue (lymph tissue involvement).

4.3 Ibrutinib is an orally administered small molecule inhibitor of Bruton's tyrosine kinase. In B cells, BTK signalling results in activation of pathways involved in B-cell proliferation, trafficking, chemotaxis, and adhesion.

4.4 Venetoclax is an orally bioavailable, selective inhibitor of B-cell lymphoma 2 (BCL2). In CLL, overexpression of BCL2 is associated with impairment of apoptosis, tumour cell survival, and resistance to chemotherapy.

4.5 The recommended treatment regimen for ibrutinib + venetoclax is as follows:

- Ibrutinib 420 mg administered orally once daily as a single-agent lead-in for 3 cycles (where each cycle is 28 days), then continued in combination with venetoclax for a further 12 cycles.
- Venetoclax administered orally once daily starting with a 5-week dose ramp-up (20 mg for 1 week followed by 1 week at each dose level of 50 mg, 100 mg, 200 mg), and then continued at the recommended daily dose of 400 mg; added to ongoing ibrutinib therapy commencing in Cycle 4 and continued for a total of 12 cycles.

4.6 The resubmission positioned fixed duration (FD) ibrutinib + venetoclax as an alternative treatment option to the available PBS-listed treatment options for previously untreated CLL/SLL, including fixed duration venetoclax + obinutuzumab, fixed duration chlorambucil + obinutuzumab, treat-to-progression zanubrutinib, and fixed duration fludarabine + cyclophosphamide + rituximab. The resubmission stated that ibrutinib + venetoclax will provide an all-oral fixed duration treatment alternative to the combinations that include IV obinutuzumab.

4.7 While ibrutinib + venetoclax is included as a recommended treatment option for patients with previously untreated CLL/SLL in the November 2023 National Comprehensive Cancer Network guidelines, it is not listed as a 'preferred regimen'. Preferred regimens for first-line treatment of patients with CLL/SLL (regardless of del(17p)/TP53 mutation status) include acalabrutinib +/- obinutuzumab, venetoclax + obinutuzumab and zanubrutinib.

4.8 The 2022 British Society for Haematology guidelines state that the relatively high incidence of early treatment-related mortality in ibrutinib + venetoclax treated patients compared with the control arm in the GLOW trial and ibrutinib + venetoclax patients in the CAPTIVATE study suggests this combination should be used with

caution in older/more comorbid patients, and should be limited to fit patients with high-risk CLL.

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

5 Comparator

5.1 The resubmission nominated fixed duration treatment with venetoclax + obinutuzumab as the main comparator. The main arguments provided in support of this nomination were:

- Venetoclax + obinutuzumab is the most widely used treatment option in patients with previously untreated CLL.
- Ibrutinib + venetoclax and venetoclax + obinutuzumab both include venetoclax as a main component and are both administered as a fixed duration regimen.
- The PBAC previously considered that, should venetoclax + obinutuzumab be listed for all patients regardless of suitability for fludarabine based chemoimmunotherapy, and regardless of CIRS score, there may be a degree of overlap with the likely patient population for ibrutinib + venetoclax (para 7.10, ibrutinib Public Summary Document (PSD), December 2022 intracycle PBAC meeting).

5.2 The resubmission nominated treat-to-progression zanubrutinib as a secondary/ supplementary comparator, noting that it was listed on the PBS on 1 September 2023 for use in patients with previously untreated CLL/SLL. Zanubrutinib was listed on the basis of a cost-minimisation approach to venetoclax + obinutuzumab.

5.3 The resubmission identified acalabrutinib +/- obinutuzumab as a near market comparator, given that it received a positive recommendation at the July 2023 PBAC meeting based on a cost-minimisation approach versus venetoclax + obinutuzumab. The resubmission stated that a comparison with acalabrutinib +/- obinutuzumab was not included in the current resubmission, as the results for zanubrutinib could be considered representative of treat-to-progression therapy with available BTK inhibitors.

5.4 The evaluation and the ESC considered the nominated comparators to be appropriate.

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 (64), health care

professionals (6) and from the three organisations, the Leukaemia Foundation, Lymphoma Australia, and Rare Cancers Australia, via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with ibrutinib + venetoclax including improved quality of life due to reduced fatigue, an ability to work and improved mental health, and the potential for complete disease remission. Potential safety concerns were noted by health professionals including immunosuppression, AF and bleeding; however, some current patients noted minimal side effects. Most respondents noted that, as a time-limited, all-oral combination therapy, ibrutinib + venetoclax (compared with IV infusion obinutuzumab + oral venetoclax): (i) improves patient access and convenience given there is no need for in-hospital/clinic treatment or time away from work for infusions, and (ii) provides more equitable access for rural and remote patients. Comments from the Leukaemia Foundation and Lymphoma Australia also highlighted the benefits of an all-oral regimen.

Clinical studies

6.3 No head-to-head trials comparing ibrutinib + venetoclax to the nominated comparators were identified in the resubmission's literature search.

6.4 The resubmission was based on the following comparisons of ibrutinib + venetoclax to the nominated comparators:

- A Bucher method indirect comparison of efficacy outcomes for ibrutinib + venetoclax (GLOW) versus venetoclax + obinutuzumab (CLL-14) using chlorambucil + obinutuzumab as the common reference.
- An unanchored matching adjusted indirect comparison (MAIC) of efficacy outcomes for ibrutinib + venetoclax (GLOW) versus venetoclax + obinutuzumab (CLL-14).
- An unanchored MAIC of efficacy outcomes for ibrutinib + venetoclax (GLOW) versus zanubrutinib (SEQUOIA).
- An unanchored unadjusted (naïve) indirect treatment comparison of safety outcomes for ibrutinib + venetoclax (GLOW) versus venetoclax + obinutuzumab (CLL-14).
- An unanchored unadjusted (naïve) indirect treatment comparison of safety outcomes for ibrutinib + venetoclax (GLOW) versus zanubrutinib (SEQUOIA).

6.5 Details of the trials presented in the resubmission are provided in Table 3.

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Indirect randomised trials		
Ibrutinib trials		
GLOW	A randomized, open-label, phase 3 study of the combination of ibrutinib plus venetoclax versus chlorambucil plus obinutuzumab for the first-line treatment	Clinical study reports, 12 November 2021; 22 June 2023. Patient-Reported

Trial ID	Protocol title/ Publication title	Publication citation
	of subjects with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).	Outcomes Supplemental Analyses Report, 29 September 2021.
	Munir T, Moreno C, Owen C, Follows G, et al. Impact of minimal residual disease on progression-free survival outcomes after fixed-duration ibrutinib-venetoclax versus chlorambucil-obinutuzumab in the GLOW study.	Journal of Clinical Oncology 2023; 41(21): 3689.
	Munir T, Moreno C, Owen C, Follows G, et al. CLL-106 first prospective data on minimal residual disease outcomes after fixed-duration ibrutinib plus venetoclax versus chlorambucil plus obinutuzumab for first-line treatment of CLL in older adult or unfit patients: the GLOW study.	Clinical Lymphoma Myeloma and Leukemia 2022; 22(Supplement 2): S264-S265.
	Munir T, Moreno C, Owen C, Follows GA et al. First prospective data on minimal residual disease (MRD) outcomes after fixed-duration ibrutinib plus venetoclax (Ibr+ Ven) versus chlorambucil plus obinutuzumab (Clb+ O) for first-line treatment of CLL in elderly or unfit patients: the Glow study.	Blood 2021; 138(Supplement 1): 70.
CAPTIVATE	Phase 2 study of the combination of ibrutinib plus venetoclax in subjects with treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma.	Clinical study reports, 11 November 2021; 28 March 2023; 19 June 2023.
	Tam, CS, Allan, JN, Siddiqi T, Kipps TJ, et al. Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary analysis of the CAPTIVATE FD cohort.	Blood. 2022; 139(22): 3278-3289.
	Moreno C, Solman IG, Tam CS, Grigg A, et al. Immune restoration with ibrutinib plus venetoclax in first-line chronic lymphocytic leukemia: the phase 2 CAPTIVATE study.	Blood Adv 2023; 7(18): 5294-5303.
	Allan J.N., Flinn I.W., Siddiqi T., Ghia P., Outcomes in Patients with High-Risk Features after Fixed-Duration Ibrutinib plus Venetoclax: Phase II CAPTIVATE Study in First-Line Chronic Lymphocytic Leukemia.	Clinical Cancer Research 2023; 29(14): 2593-2601.
	Barr PM, Tedeschi A, Wierda WG, Allan JN, et al. Effective Tumor Debulking with Ibrutinib Before Initiation of Venetoclax: Results from the CAPTIVATE Minimal Residual Disease and Fixed-Duration Cohorts.	Clinical Cancer Research 2022; 28(20): 4385-4391.
Venetoclax + obinutuzumab trial		
CLL-14	Fischer K, Al-Sawaf O, Bahlo J, Fink AM, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions.	New England Journal of Medicine 2019; 380(23): 2225-2236.
	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.	The Lancet Oncology 2020; 21(9): 1188-1200.
	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.	Journal of Clinical Oncology 2021; 39(36): 4049-4060.
	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.	American Journal of Hematology 2021; 96(9): 1112-1119.

Trial ID	Protocol title/ Publication title	Publication citation
Zanubrutinib trial		
SEQUIOA	Munir T, Shadman M, Robak T, Brown JR, et al. Zanubrutinib (zanu) vs bendamustine + rituximab (BR) in patients (pts) with treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): extended follow-up of the SEQUOIA study	Hemasphere 2023; 7(S3): e15364af.
	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.	The Lancet Oncology 2022; 23(8): 1031-1043.
	Tam CS, Robak T, Ghia P, Kahl BS, et al. Zanubrutinib monotherapy for patients with treatment naïve chronic lymphocytic leukaemia and 17p deletion.	Haematologica 2020; 106(9): 2354-2363.
	Ghia P, Barnes G, Yang K, Tam CS, et al. Health-related quality-of-life in treatment-naive CLL/SLL patients treated with zanubrutinib versus bendamustine plus rituximab.	Cancer Medicine 2023; 12(18): 18643-18653.
	Brown JR, Robak T, Ghia P, Kahl BS, et al. Efficacy and safety of zanubrutinib in patients with treatment-naïve (TN) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) with del(17p): follow-up results from arm C of the SEQUOIA (BGB-3111-304) trial.	Blood 2020; 136:11-12.

Source: Table 1.11 of the resubmission.
Selected citations relating to conference abstracts omitted.

6.6 The key features of the GLOW, CAPTIVATE, CLL-14 and SEQUOIA trials are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Ibrutinib + venetoclax versus chlorambucil + obinutuzumab					
GLOW	211	Phase 3, open-label, randomised trial. Median follow-up: 52.1 months.	Unclear	- Age ≥65 years, or age 18 to 64 years meeting additional criteria (CrCl <70 mL/min or CIRS score >6). - Diagnosis of CLL or SLL that meets iwCLL criteria. - Active CLL/SLL requiring treatment as per iwCLL criteria. - Measurable nodal disease. - No prior anti-leukemic therapy for CLL or SLL - Patients with 17p deletion or known TP53 mutation detected at a threshold of >10% variable allele frequency were excluded.	- PFS - MRD negativity in bone marrow - CRR - ORR - OS - TTNT - Adverse events - HRQOL (EORTC QLQ-C30, FACIT-Fatigue scale, EQ-5D-5L).
Ibrutinib + venetoclax					
CAPTIVATE (fixed duration cohort)	159	Single-arm, open-label study. Median follow-up: 55.7 months	High	- Age 18 to 70 years. - ECOG performance status of 0-2. - Diagnosis of CLL/SLL meeting iwCLL diagnostic criteria. - Active disease meeting ≥1 iwCLL criteria for requiring treatment. - Measurable nodal disease - No prior therapy used for treatment of CLL or SLL.	- Best overall response of CR or CRi - ORR - Duration of response - MRD negativity rate - Tumour lysis syndrome risk reduction - Adverse events
Venetoclax + obinutuzumab versus chlorambucil + obinutuzumab					

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
CLL-14	432	Phase 3, open-label, randomised trial. Median follow-up: 76.4 months.	Unclear	- Age ≥18 years. - CIRS score >6 or CrCl <70 mL/min. - Life expectancy >6 months - CLL requiring treatment according to the iwCLL 2008 criteria. - Documented previously untreated CLL according to iwCLL criteria.	- PFS - ORR - CRR - MRD response rate - OS - Duration of response - TTNT - Event-free survival - Adverse events - HRQOL (MDASI, EORTC QLQ-C30, EQ-5D-5L).
Zanubrutinib versus bendamustine + rituximab					
SEQUOIA	590	Phase 3, open-label, randomised trial. Median follow-up: 43.7 months.	Unclear	- Age ≥65 years, or age 18 to 64 years meeting additional criteria (CrCl of 30 to 69 mL/min, CIRS score >6, or history of previous serious infection or multiple infections in the past 2 years). - ECOG score ≤2. - Confirmed diagnosis of CD20-positive CLL or SLL meeting iwCLL criteria. - CLL/SLL requiring treatment based on iwCLL criteria. - Life expectancy ≥6 months. - Measurable disease. - No previous systemic treatment for CLL/SLL.	- PFS - ORR - Duration of response - OS - Adverse events - HRQOL (MDASI-CLL, EORTC QLQ-C30, EQ-5D-3L).

Source: Section 2.3 of the resubmission; Table 2.20; Section 2.4.2; Section 2.4.3 of the resubmission.
Abbreviations: CIRS, cumulative illness rating scale; CLL, chronic lymphocytic leukaemia; CR, complete response; CrCl, creatinine clearance; CRi, complete response with incomplete bone marrow recovery; CRR, complete response rate; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; FACIT, Functional Assessment of Chronic Illness Therapy; HRQOL, health-related quality of life; iwCLL, International Workshop on Chronic Lymphocytic Leukaemia; MDASI, MD Anderson Symptom Inventory; MRD, minimal residual disease; ORR, overall response rate; QLQ, quality of life questionnaire; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SLL, small lymphocytic lymphoma; TTNT, time to next treatment.

6.7 The GLOW trial is an ongoing international trial comparing treatment with ibrutinib + venetoclax versus chlorambucil + obinutuzumab in patients with previously untreated CLL/SLL. Results for the primary analysis (February 2021 data cut: median follow-up of 27.7 months) and two interim analyses (August 2022 data cut: median follow-up 46.1 months; February 2023 data cut: median follow-up 52.0 months) were presented in the resubmission. The GLOW trial was excluded from the November 2022 ibrutinib submission on the basis that the trial population differed from the proposed PBS population (patients who had a CIRS score ≤6 and a creatinine clearance ≥70 mL/min).

6.8 The CAPTIVATE study is an ongoing single-arm study of fixed duration ibrutinib + venetoclax. The study incorporated a fixed duration treatment cohort and an MRD-guided discontinuation cohort. Results for the fixed duration cohort at the primary analysis (December 2020 data cut; median follow-up 27.9 months) were presented as key evidence in the November 2022 submission. The resubmission included additional data from the CAPTIVATE study, corresponding to a median follow-up of 49.8 months (October 2022 data cut) and 55.7 months (March 2023 data cut).

6.9 The resubmission considered the GLOW, CLL-14 and SEQUOIA trials to have a low risk of bias, however the evaluation considered the risk of bias in the trials to be unclear/high. 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. Each trial included blinded assessments by an independent review committee, which had a lower risk of assessment bias. Assessments made by unblinded study investigators were at high risk of bias. Longer term results for the trials were generally based on investigator assessment. The CAPTIVATE study was a single-arm study, and consequently, had a high risk of bias.

6.10 The GLOW, CAPTIVATE, CLL-14 and SEQUOIA trials recruited patients with previously untreated CLL/SLL with active disease requiring treatment (the CLL-14 trial recruited patients with CLL only). Patients in the GLOW and SEQUOIA trials were aged ≥65 years, or 18 to 65 years with a CIRS score >6 or a creatinine clearance <70 mL/min. The SEQUOIA trial also included patients aged 18 to 65 years with a history of serious or multiple infections in the past 2 years. The CLL-14 trial recruited patients aged ≥ 18 years with a CIRS score >6 or creatinine clearance <70 mL/min. The CAPTIVATE study recruited patients aged 18 to 70 years, with no specified CIRS or creatinine clearance criteria, resulting in a patient population considered more "fit" for treatment with immunochemotherapy, based on fewer comorbidities. GLOW, CAPTIVATE and SEQUOIA specified an ECOG ≤2; no ECOG score was specified in the CLL-14 trial.

6.11 CAPTIVATE, SEQUOIA and CLL-14 trials included patients with 17p deletion. Patients in the SEQUOIA trial with 17p deletion were not randomised, and received treatment with zanubrutinib in a separate treatment arm. The GLOW trial excluded patients with 17p deletion or known TP53 mutation detected at a threshold of >10% variable allele frequency.

6.12 Patients in the ibrutinib + venetoclax arm of the GLOW trial and the fixed duration cohort of the CAPTIVATE study received 15 cycles of treatment with oral ibrutinib (420 mg daily), and 12 cycles of oral venetoclax (initial dose ramp-up cycle followed by 11 cycles of 400 mg daily). Patients in the chlorambucil + obinutuzumab arm of the GLOW trial received chlorambucil 0.5 mg/kg/m^2 orally on Days 1 and 15 for 6 cycles; and obinutuzumab 1,000 mg intravenously on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycles 2 to 6. Patients in the chlorambucil + obinutuzumab arm of the CLL-14 trial received chlorambucil 0.5 mg/kg/m^2 orally on Days 1 and 15 for 12 cycles; and obinutuzumab 1,000 mg intravenously on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycles 2 to 6. The median duration of chlorambucil treatment in the CLL-14 trial was substantially longer than in the GLOW trial (11.1 months versus 5.5 months).

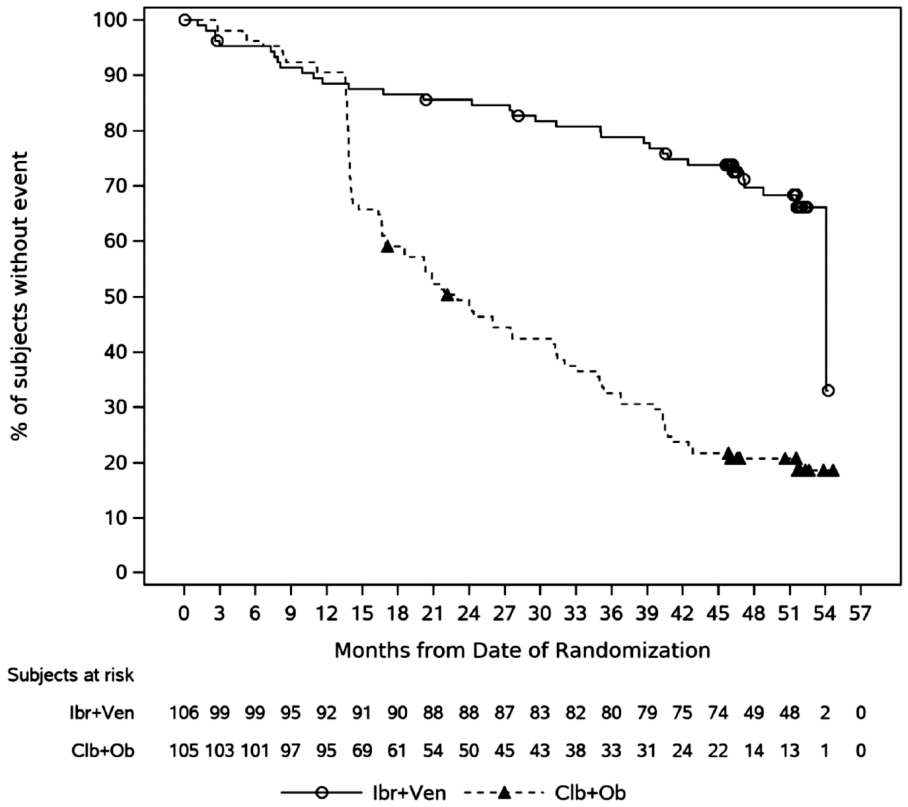
6.13 The resubmission argued that the outcomes reported by the trials, including progression-free survival, overall survival, time to next treatment, overall response rate, the rate of MRD-negative responses, and health-related quality of life are all clinically important outcomes. No clinically important differences were identified for

any of the efficacy outcomes. No non-inferiority margins were proposed in the resubmission.

Comparative effectiveness

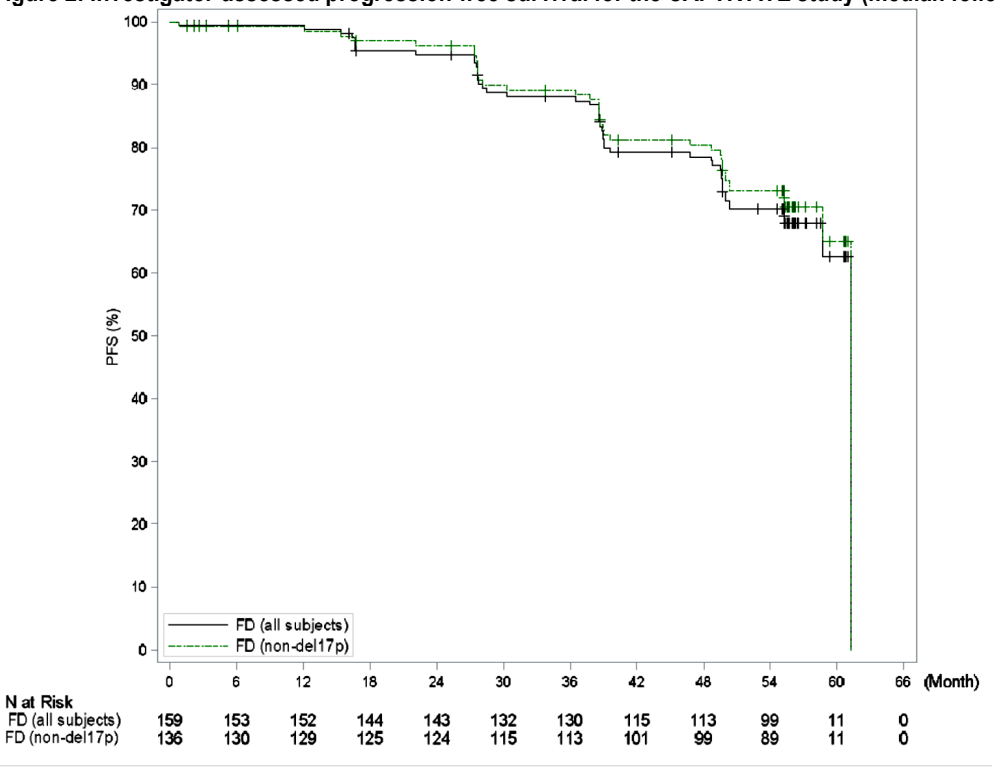
6.14 Kaplan-Meier plots of investigator-assessed progression-free survival based on extended follow-up for the GLOW trial and the CAPTIVATE study, respectively, are presented in Figure 1 and Figure 2.

Figure 1: Investigator-assessed progression-free survival for the GLOW trial (median follow-up: 52.1 months)



Source: Figure 2.12 of the resubmission.
Abbreviations: Clb, chlorambucil; Ibr, ibrutinib; Ob, obinutuzumab; Ven, venetoclax.

Figure 2: Investigator-assessed progression-free survival for the CAPTIVATE study (median follow-up: 55.7 months)



Source: Figure 2.19 of the resubmission.
Abbreviations: FD, fixed duration; PFS, progression-free survival.

6.15 Table 5 presents a summary of investigator-assessed progression-free survival results for the GLOW, CAPTIVATE, CLL-14 and SEQUOIA trials based on extended follow-up.

Table 5: Investigator-assessed progression-free survival results for GLOW, CAPTIVATE, CLL-14 and SEQUOIA

	GLOW		CAPT-IVATE	CLL-14		SEQUOIA		
	IBR + VEN	CHL + OBI	IBR + VEN	VEN + OBI	CHL + OBI	ZAN	ZAN (del 17p)	BEN + RIT
	N=106	N=105	N=159	N=216	N=216	N=241	N=110	N=238
Median follow-up, months (range)	52.1 (1.7-56.4)	51.9 (5.1-57.8)	55.7 (0.8-61.2)	65.4 (IQR 52.6-69.4)		43.7 (0-60.0)		47.9 (5.0-56.9)
Events, n (%)	33 (31.1)	83 (79.0)	48 (30.2)	80 (37.0)	150 (69.4)	NR	NR	NR
- Progression	20 (18.9)	75 (71.4)	45 (28.3)	52 (24.1)	132 (61.1)	NR	NR	NR
- Death	13 (12.3)	8 (7.6)	3 (1.9)	28 (13.0)	18 (8.3)	NR	NR	NR
Median PFS, months (95% CI)	54.1 (54.1, NE)	23.0 (16.9, 31.2)	61.2 (58.7, NE)	76.2 (NR)	36.4 (NR)	NE (NR)	NE (NR)	42.2 (NR)
HR vs comparator (95% CI)	**0.23 (0.15, 0.35)**	-	-	**0.35 (0.26, 0.46)**	**-**	**0.30 (0.21, 0.43)**		**-**
KM estimate of PFS								
- 36 months, % (95% CI)	78.8 (69.5, 85.5)	32.6 (23.8, 41.7)	88.1 (81.7, 92.3)	NR	NR	NR	NR	NR
- 42 months, % (95% CI)	74.8 (65.2, 82.1)	23.7 (16.0, 32.3)	79.2 (71.8, 84.9)	NR	NR	82.4 (NR)	79.4 (NR)	50.0 (NR)
- 48 months, % (95% CI)	69.7 (59.5, 77.9)	20.7 (13.4, 29.0)	78.5 (71.0, 84.3)	74.0 (NR)[a]	35.4 (NR)[a]	-	-	-
- 54 months, % (95% CI)	66.1 (55.0, 75.1)	18.6 (11.4, 27.3)	70.2 (62.0, 76.9)	NR	NR	-	-	-
- 60 months, % (95% CI)	-	-	62.7 (49.3, 73.5)	62.6 (55.7, 69.6)	27.0 (20.6, 33.4)	-	-	-

Source: Table 1, p9 of the GLOW clinical study report (February 2023 data cut); Table 4, p15 of the CAPTIVATE clinical study report (March 2023 data cut); p2 of Al-Sawaf et al. (2023); Munir et al. (2023).

Abbreviations: CHL, chlorambucil; CI, confidence interval; HR, hazard ratio; IBR, ibrutinib; OBI, obinutuzumab; PFS, progression-free survival; RIT, rituximab; VEN, venetoclax.

[a] Reported by Al-Sawaf et al. (2021) based on a median follow-up of 52.4 months.

6.16 Based on extended follow-up, median progression-free survival was 54.1 months in the ibrutinib + venetoclax arm of the GLOW trial and 23.0 months in the chlorambucil + obinutuzumab arm. Treatment with ibrutinib + venetoclax was associated with a statistically significant improvement in investigator-assessed progression-free survival compared to chlorambucil + obinutuzumab (hazard ratio: 0.23; 95% CI: 0.15, 0.35).

6.17 Based on extended follow-up, the median progression-free survival was 61.2 months in the ibrutinib + venetoclax arm of the CAPTIVATE study.

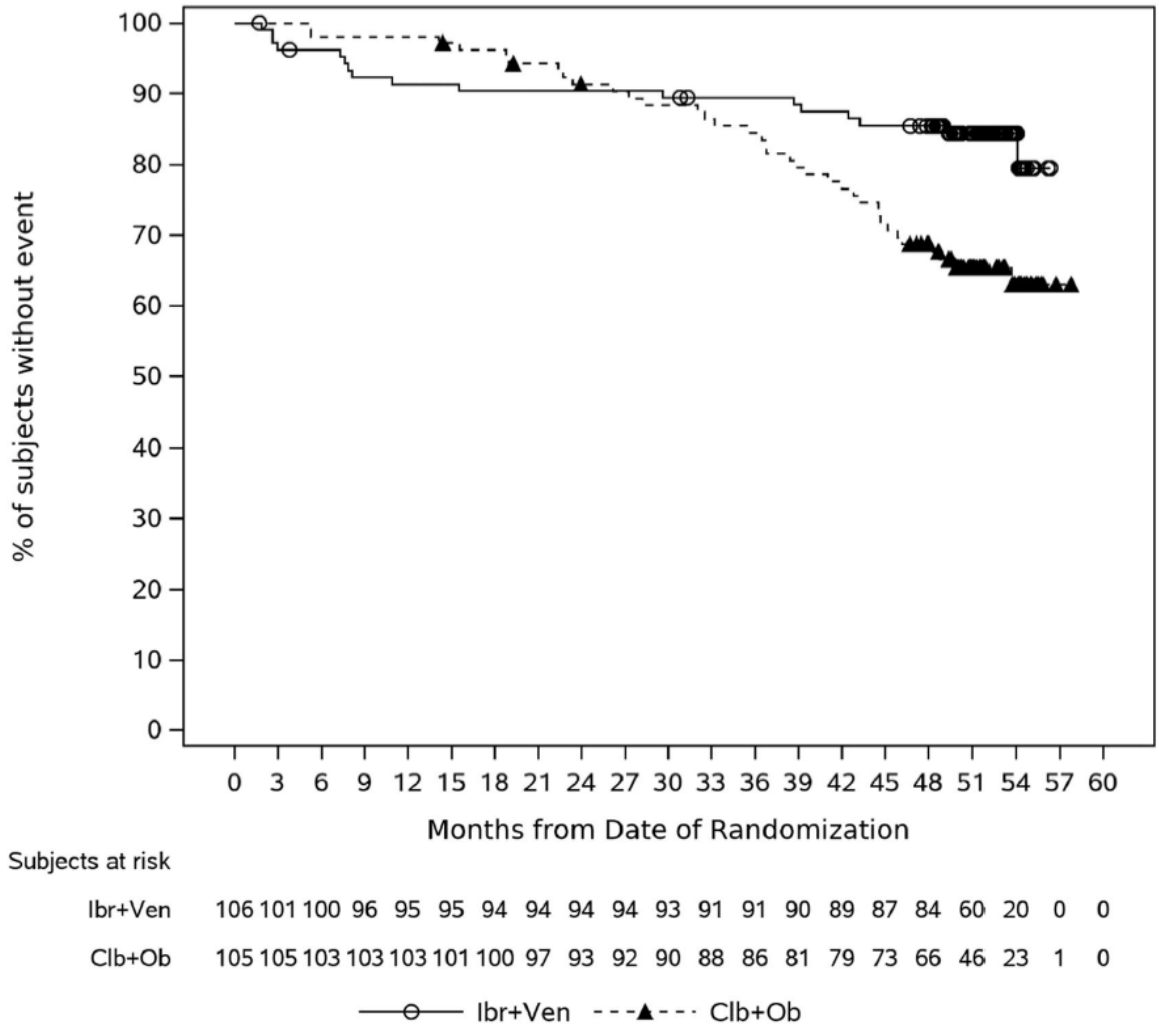
6.18 Based on a naïve comparison of investigator-assessed progression-free survival, the proportion of patients remaining progression-free at 48 months was 69.7% in the ibrutinib + venetoclax arm of the GLOW trial, 78.5% in the ibrutinib + venetoclax arm of the CAPTIVATE study and 74.0% in the venetoclax + obinutuzumab arm of the CLL-14 trial. The PBAC noted however, that there was a substantial difference in the Kaplan-Meier estimates of PFS at 48 months in the common comparator arms of the GLOW and CLL-14 trials (20.7% versus 35.4%, respectively).

6.19 The proportion of patients remaining progression-free at 42 months was 74.8% in the ibrutinib + venetoclax arm of the GLOW trial, 79.2% in the ibrutinib + venetoclax arm

of the CAPTIVATE study, and 82.4%/79.4% in the zanubrutinib arms of the SEQUOIA trial (without 17p deletion and with 17p deletion, respectively).

6.20 Kaplan-Meier plots of overall survival based on extended follow-up for the GLOW trial and the CAPTIVATE study, respectively, are presented in Figure 3 and Figure 4.

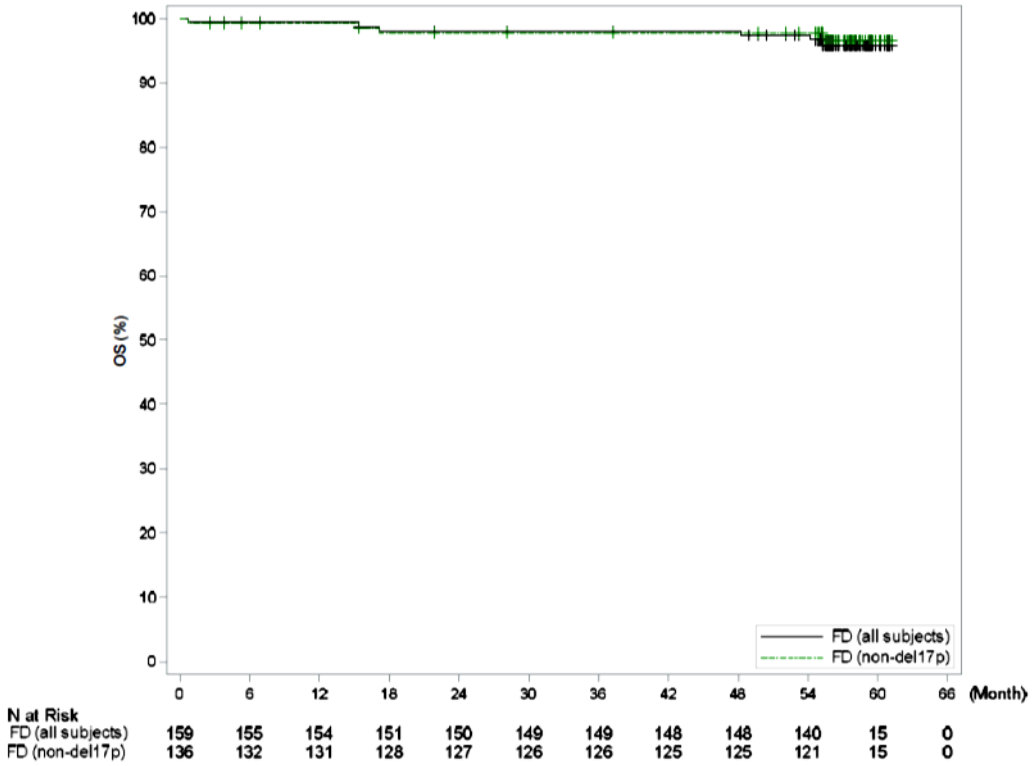
Figure 3: Overall survival results for the GLOW trial (median follow-up: 52.1 months)



Source: Figure 2.14 of the resubmission.
Abbreviations: Clb, chlorambucil; Ibr, ibrutinib; Ob, obinutuzumab; Ven, venetoclax.

6.21 The proportion of surviving patients in the GLOW trial was notably lower in the ibrutinib + venetoclax arm compared to the chlorambucil + obinutuzumab arm during the initial two years. However, the survival curves subsequently cross at approximately 26 months, from which time the proportion of surviving patients in the ibrutinib + venetoclax arm is higher.

Figure 4: Overall survival results for the CAPTIVATE study (median follow-up: 55.7 months)



Source: Figure 2.20 of the resubmission.
Abbreviations: FD, fixed duration; OS, overall survival.

6.22 Table 6 presents the overall survival results for the GLOW, CAPTIVATE, CLL-14 and SEQUOIA trials.

Table 6: Overall survival results for the GLOW, CAPTIVATE, CLL-14 and SEQUOIA trials

	GLOW		CAPTI-VATE	CLL-14		SEQUOIA		
	IBR + VEN	CHL + OBI	IBR + VEN	VEN + OBI	CHL + OBI	ZAN	ZAN (del 17p)	BEN + RIT
	N=106	N=105	N=159	N=216	N=216	N=241	N=110	N=238
Median follow-up, months (range)	52.1 (1.7-56.4)	51.9 (5.1-57.8)	55.7 (0.8-61.2)	76.4 (NR)		43.7 (0-60.0)		47.9 (5.0-56.9)
Events, n (%)	17 (16.0)	36 (34.3)	6 (3.8)	48 (NR)	70 (NR)	NR	NR	NR
Median OS, months (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NR)	NE (NR)	NE (NR)	NE (NR)	NE (NR)
HR vs comparator (95% CI)	**0.46 (0.26, 0.82)**	-	-	**0.69 (0.48, 1.01)**	-	**0.87 (0.50, 1.48)**	-	-
KM estimate of OS								
- 42 months, % (95% CI)	87.5 (79.4, 92.5)	77.6 (68.2, 84.5)	98.1 (94.2, 99.4)	NR	NR	89.4 (NR)	89.5 (NR)	88.3 (NR)
- 48 months, % (95% CI)	85.5 (77.1, 91.0)	68.8 (58.8, 76.8)	98.1 (94.2, 99.4)	85.4 (NR)[a]	83.1 (NR)[a]	-	-	-
- 54 months, % (95% CI)	84.4 (75.8, 90.1)	63.0 (52.0, 72.2)	97.4 (93.3, 99.0)	NR	NR	-	-	-
- 60 months, % (95% CI)	-	-	95.8 (90.8, 98.1)	NR	NR	-	-	-
- 66 months, % (95% CI)	-	-	-	NR	NR	-	-	-
- 72 months, % (95% CI)	-	-	-	78.7 (NR)	69.2 (NR)	-	-	-

Source: Table 3, p15 of the GLOW clinical study report (February 2023 data cut); Table 5, p17 of the CAPTIVATE clinical study report (March 2023 data cut); Slide 18 of Al-Sawaf et al. (2023) conference slides; Munir et al. (2023).
Abbreviations: CHL, chlorambucil; CI, confidence interval; HR, hazard ratio; IBR, ibrutinib; OBI, obinutuzumab; OS, overall survival; RIT, rituximab; VEN, venetoclax; ZAN, zanubrutinib.
[a] Reported by Al-Sawaf et al. (2021) based on a median follow-up of 52.4 months.

6.23 Based on extended follow-up, median overall survival was not reached in either arm of the GLOW trial. Treatment with ibrutinib + venetoclax was associated with a statistically significant improvement in overall survival compared to treatment with chlorambucil + obinutuzumab (hazard ratio: 0.46; 95% CI: 0.26, 0.82).

6.24 Based on extended follow-up, the median overall survival in the ibrutinib + venetoclax arm of the CAPTIVATE study was not reached.

6.25 Based on a naïve comparison of overall survival, the proportion of patients remaining alive at 48 months was 85.5% in the ibrutinib + venetoclax arm of the GLOW trial, 98.1% in the ibrutinib + venetoclax arm of the CAPTIVATE study and 85.4% in the venetoclax + obinutuzumab arm of the CLL-14 trial. The PBAC noted however, that there was a substantial difference in the Kaplan-Meier estimates of overall survival at 48 months in the common comparator arms of the GLOW and CLL-14 trials (68.8% versus 83.1%, respectively).

6.26 The proportion of patients remaining alive at 42 months was 87.5% in the ibrutinib + venetoclax arm of the GLOW trial, 98.1% in the ibrutinib + venetoclax arm of the CAPTIVATE study and 89.4%/89.5% in the zanubrutinib arms of the SEQUOIA trial (without 17p deletion and with 17p deletion, respectively).

Bucher method indirect comparison

6.27 The resubmission presented a Bucher method indirect comparison of ibrutinib + venetoclax (GLOW) versus venetoclax + obinutuzumab (CLL-14), using chlorambucil + obinutuzumab as the common reference.

6.28 The resubmission noted the planned number of chlorambucil cycles administered in the CLL-14 trial (12 cycles) differed from the planned number of chlorambucil cycles in the GLOW trial (6 cycles). The resubmission also noted that the PBAC previously considered, in the context of the November 2017 submission for ibrutinib, that variations in the chlorambucil dosing when used as a common comparator was not a significant issue (para 6.8, ibrutinib PSD, November 2017 PBAC meeting). The resubmission considered that the previous PBAC consideration may not necessarily apply in the context of the GLOW and CLL-14 trials, given that the median chlorambucil exposure in CLL-14 (11.1 months) was approximately twice the median exposure in the GLOW trial (5.1 months), and there were notable differences in the trajectories of the progression-free survival Kaplan-Meier curves for the chlorambucil + obinutuzumab arms of the trials. Based on these differences, the evaluation considered the use of chlorambucil + obinutuzumab as a common reference for an indirect comparison did not appear to be appropriate, and is likely to favour ibrutinib + venetoclax given the shorter progression-free survival for the chlorambucil + obinutuzumab arm in the GLOW trial.

6.29 Comparisons were presented for investigator-assessed progression-free survival, overall survival, time to next treatment, complete response and overall response. The comparisons for progression-free survival, overall survival and time to next treatment were based on results for the CLL-14 trial reported by Al-Sawaf et al. (2021; median follow-up 52.4 months). An additional comparison incorporating the most recent data reported for the CLL-14 trial (Al-Sawaf et al., 2023; median follow-up of 76.4-months) was presented as a sensitivity analysis. Comparisons of complete and overall response were based on a median follow-up of 27.7 months for the GLOW trial and 28.1 months for CLL-14. An additional comparison incorporating GLOW trial data corresponding to a median follow-up of 46.1 months was included as a sensitivity analysis.

6.30 Table 7 presents the results for the indirect comparison of investigator-assessed progression-free survival.

Table 7: Results for the indirect comparison of investigator-assessed progression-free survival

Trial	Outcome	IBR + VEN n/N (%)	CHL + OBI n/N (%)	Absolute difference	HR (95% CI)
GLOW	Progressed	33/106 (31.1)	83/105 (79.0)	47.9%	**0.23 (0.15, 0.35)**
	Median months PFS	54.1 (54.1, NE)	23.0 (16.9, 31.2)	31.1 months	
Comparator		**VEN + OBI n/N (%)**	**CHL + OBI n/N (%)**	**Absolute difference**	**HR (95% CI)**
CLL-14	Progressed	61 (28.2)	NR	NE	**0.33 (0.25, 0.45)**
	Median months PFS	NE (NE, NE)	36.4 (NR, NR)	NE	
Indirect comparison IBR + VEN vs. VEN + OBI					0.69 (0.42, 1.16)
Sensitivity analysis[a]					**0.57 (0.35, 0.94)**

Source: Table 2.85; Table 2.86 of the resubmission.
Abbreviations: CHL, chlorambucil; HR, hazard ratio; IBR, ibrutinib; NE, not estimable; NR, not reported; OBI, obinutuzumab; PFS, progression-free survival; VEN, venetoclax.
[a] Sensitivity analysis conducted using data from the CLL-14 trial corresponding to a median follow-up of 76.4 months.
Bold indicates statistically significant results.

6.31 Based on the indirect comparison, treatment with ibrutinib + venetoclax was associated with improvement in progression-free survival compared to venetoclax + obinutuzumab, however, the difference was not statistically significant (hazard ratio: 0.69; 95% CI: 0.42, 1.16).

6.32 Table 8 presents the results for the indirect comparison of overall survival.

Table 8: Results for the indirect comparison of overall survival

Trial	Outcome	IBR + VEN n/N (%)	CHL + OBI n/N (%)	Absolute difference	HR (95% CI)
GLOW	Death	17/106 (16.0)	36/105 (34.3)	18.3%	**0.46 (0.26, 0.82)**
	Median months OS	NE (NE, NE)	NE (NE, NE)	NE	
Comparator		**VEN + OBI n/N (%)**	**CHL + OBI n/N (%)**	**Absolute difference**	**HR (95% CI)**
CLL-14	Death	34 (15.7)	41 (19.0)	NE	0.85 (0.54, 1.35)
	Median months OS	NE (NE, NE)	NE (NE, NE)	NE	
Indirect comparison IBR + VEN vs. VEN + OBI					0.54 (0.26, 1.13)
Sensitivity analysis[a]					0.66 (0.33, 1.32)

Source: Table 2.87; Table 2.88 of the resubmission.
Abbreviations: CHL, chlorambucil; HR, hazard ratio; IBR, ibrutinib; NE, not estimable; NR, not reported; OBI, obinutuzumab; OS, overall survival; VEN, venetoclax.
[a] Sensitivity analysis conducted using data from the CLL-14 trial corresponding to a median follow-up of 76.4 months.
Bold indicates statistically significant results.

6.33 Based on the indirect comparison, treatment with ibrutinib + venetoclax was associated with improved overall survival compared to venetoclax + obinutuzumab, however, the difference was not statistically significant (hazard ratio: 0.54; 95% CI: 0.26, 1.13).

6.34 Treatment with ibrutinib + venetoclax was associated with a longer time to next treatment compared to venetoclax + obinutuzumab, and the difference was statistically significant (hazard ratio: 0.36; 95% CI: 0.16, 0.78). Treatment with ibrutinib + venetoclax was associated with a higher complete response rate (odds ratio: 1.65; 95% CI: 0.74, 3.66) and a lower overall response rate (odds ratio: 0.78; 95% CI: 0.27, 2.19) compared to venetoclax + obinutuzumab, but the differences were not statistically significant.

Matching adjusted indirect comparisons

6.35 The resubmission presented unanchored MAICs of ibrutinib + venetoclax versus venetoclax + obinutuzumab and ibrutinib + venetoclax versus zanubrutinib. The resubmission stated that the unanchored MAIC of ibrutinib + venetoclax versus venetoclax + obinutuzumab was included due to differences in the dosing schedule and exposure of chlorambucil in the chlorambucil + obinutuzumab arms of the GLOW and CLL-14 trials. There was limited documentation describing the methodology used to conduct the MAICs. No technical document was provided.

6.36 The resubmission stated that eight prognostic factors were selected for matching in the main analysis (median age, TP53 mutation status, Binet Stage A or B, serum β2-microglobulin >3.5 mg/L, IGHV mutation status, median time from diagnosis to randomisation, gender and ECOG status). The resubmission stated that the first five variables (median age, TP53 mutation status, Binet Stage A or B, serum β2-microglobulin >3.5 mg/L, IGHV mutation status) were identified and chosen based on international consensus on key prognostic factors (International CLL-IPI working group; 2016). The resubmission stated that other baseline characteristics (median time from diagnosis to randomisation, gender, and ECOG status) were included due to the consistent availability of these across the trials. The resubmission included an additional analysis in which only five of the selected variables were matched: median age, TP53 mutation status, Binet Stage A or B, serum β2-microglobulin >3.5 mg/L, IGHV mutation status.

6.37 Details of any literature searches to identify prognostic variables and treatment effect modifier variables were not presented. It is unclear whether all relevant prognostic and treatment effect modifier variables were identified and included for matching. The resubmission referred to the eight matched variables as eight 'prognostic variables'. It is unclear whether the resubmission specifically included both prognostic variables and treatment effect modifiers in the MAIC. As the analysis (including the selection of variables for matching) was conducted post hoc, the results of the MAICs had a high risk of bias.

6.38 The PSCR noted the concerns raised in the commentary regarding the limited number of variables included for matching in the unanchored MAICs, and reiterated (i) the methodology used to identify the variables, (ii) the consistency of the results when either 5 or 8 variables were used in the analysis, and (iii) the consistency of the MAIC approach used with the MAICs considered by the PBAC when it recommended zanubrutinib, and acalabrutinib, on a non-inferiority basis to V+O in March 2023 and July 2023. In addition, the PSCR argued that the inclusion of additional variables for matching would further reduce the effective sample size.

6.39 The evaluation considered that, ideally, an unanchored MAIC should adjust for all relevant treatment effect modifier and prognostic variables to reliably predict outcomes and that the small effective sample size after matching likely reflects

differences in patient populations between the trials, as well as the relatively small number of patients in the ibrutinib + venetoclax arm of the GLOW trial (N=106).

6.40 The main analysis for each outcome was based on the restricted mean survival time. The resubmission stated that restricted mean survival time was used on the basis that the proportional hazard assumption was violated in each of the comparisons. Details of the assessment of the proportional hazards assumption were not presented in the resubmission. Results derived based on hazard ratio estimates were also included in the resubmission.

Ibrutinib + venetoclax versus venetoclax + obinutuzumab

6.41 Data for the ibrutinib + venetoclax arm of the GLOW trial included in the unanchored MAIC were based on the February 2023 data cut, with a median follow-up of 52.1 months. Data for the venetoclax + obinutuzumab arm of the CLL-14 trial was based on Al-Sawaf et al. (2021), corresponding to a median duration of follow-up of 52.4 months.

6.42 Results of the unanchored MAIC of progression-free survival and overall survival for ibrutinib + venetoclax versus venetoclax + obinutuzumab are presented in Table 9.

Table 9: Results of the unanchored MAICs for ibrutinib + venetoclax versus venetoclax + obinutuzumab

Analysis	RMST difference (95% CI)	p-value
Investigator-assessed progression-free survival		
Unadjusted RMST (N=106)	-2.71 (-6.84,1.42)	0.198
Adjustment based on 8 prognostic variables (primary analysis; ESS=53)	-0.81 (-5.80, 4.18)	0.750
Adjustment based on 5 prognostic variables (sensitivity analysis; ESS=62)	-0.98 (-5.80, 3.84)	0.690
Overall survival		
Unadjusted RMST (N=106)	-1.04 (-4.43, 2.35)	0.549
Adjustment based on 8 prognostic variables (primary analysis; ESS=53)	0.26 (-3.84, 4.35)	0.903
Adjustment based on 5 prognostic variables (sensitivity analysis; ESS=62)	-0.27 (-4.27, 3.74)	0.896

Source: Table 2.94; Table 2.95 of the resubmission.
Abbreviations: CI, confidence interval; ESS, effective sample size; RMST, restricted mean survival time.
A restricted mean survival time greater than zero favours ibrutinib + venetoclax.

6.43 Prior to MAIC adjustment (i.e., based on a naïve comparison of ibrutinib + venetoclax and venetoclax + obinutuzumab), the comparison of progression-free survival favoured venetoclax + obinutuzumab, but was not statistically significant (restricted mean survival time: -2.71; 95% CI: -6.84, 1.42). After MAIC adjustment for 8 prognostic variables, the difference in progression-free survival between ibrutinib + venetoclax and venetoclax + obinutuzumab remained not statistically significant (restricted mean survival time: -0.81; 95% CI: -5.80, 4.18*).* A similar result was seen after adjustment for only 5 prognostic variables (restricted mean survival time: -0.98; 95% CI: -5.80, 3.84).

6.44 Prior to MAIC adjustment (i.e., based on a naïve comparison of ibrutinib + venetoclax and venetoclax + obinutuzumab), the comparison of overall survival favoured venetoclax + obinutuzumab, but was not statistically significant (restricted mean survival time: -1.04; 95% CI: -4.45, 2.35). After MAIC adjustment for 8 prognostic variables, the difference in overall survival between ibrutinib + venetoclax and

venetoclax + obinutuzumab favoured ibrutinib + venetoclax, but remained not statistically significant (restricted mean survival time: 0.26; 95% CI: -3.84, 4.35). A similar result was seen after adjustment for only 5 prognostic variables (restricted mean survival time: -0.27; 95% CI: -4.27, 3.74).

6.45 The results of the MAICs were considered uncertain due to the limited number of prognostic and treatment effect modifier variables included for matching, limited documentation regarding the methodology used, differences in trial eligibility (patients with SLL; patients with 17p deletion), missing data for some patients in the CLL-14 trial (TP53 status), and the very low effective sample size after matching. Additionally, the resubmission did not propose non-inferiority margins for progression-free survival or overall survival. The lack of a statistically significant difference may not be sufficient to establish non-inferiority, as the 95% confidence intervals may include clinically important differences. The resubmission argued that there are no accepted non-inferiority margins for these outcomes, and that a similar approach was accepted by the PBAC in the consideration of zanubrutinib at the March 2023 PBAC meeting.

Ibrutinib + venetoclax versus zanubrutinib

6.46 Data for the ibrutinib + venetoclax arm of the GLOW trial included in the MAIC was based on the February 2023 data cut (based on a median follow-up of 52.1 months). Data for the zanubrutinib arm of the SEQUOIA trial was based on Tam et al. (2022), corresponding to a median duration of follow-up of 26.2 months. Additional results for the SEQUOIA trial, based on a median follow-up of 43.7 months) were recently published by Munir et al. (2023). It would have been preferable to include data from Munir et al. (2023) in the MAIC.

6.47 Results of the unanchored MAIC of progression-free survival and overall survival for ibrutinib + venetoclax versus zanubrutinib are presented in Table 10.

Table 10: Results of the unanchored MAICs for ibrutinib + venetoclax versus zanubrutinib

Analysis	RMST difference (95% CI)	p-value
Investigator-assessed progression-free survival		
Unadjusted RMST (N=106)	-1.00 (-3.54, 1.54)	0.440
Adjustment based on 8 prognostic variables (primary analysis; ESS=46)	0.37 (-2.84, 3.58)	0.821
Adjustment based on 5 prognostic variables (ESS=56)	0.04 (-3.05, 3.13)	0.980
Overall survival		
Unadjusted RMST (N=106)	-1.59 (-3.66, 0.48)	0.132
Adjustment based on 8 prognostic variables (primary analysis; ESS=46)	-0.95 (-3.69, 1.78)	0.495
Adjustment based on 5 prognostic variables (ESS=56)	-1.31 (-3.98, 1.36)	0.338

Source: Table 2.96; Table 2.97 of the resubmission.
Abbreviations: CI, confidence interval; ESS, effective sample size; RMST, restricted mean survival time.
A restricted mean survival time greater than zero favours ibrutinib + venetoclax.

6.48 Prior to MAIC adjustment (i.e., based on a naïve comparison of ibrutinib + venetoclax and zanubrutinib), the comparison of progression-free survival favoured zanubrutinib, but was not statistically significant (restricted mean survival time: -1.00; 95% CI: -3.54, 1.54). After MAIC adjustment for 8 prognostic variables, the difference in progression-

free survival favoured ibrutinib + venetoclax, but remained not statistically significant (restricted mean survival time: 0.37; 95% CI: -2.84, 3.58). A similar result was seen after adjustment for only 5 prognostic variables (restricted mean survival time: 0.04; 95% CI: -3.05, 3.13).

6.49 Prior to MAIC adjustment (i.e., based on a naïve comparison of ibrutinib + venetoclax and zanubrutinib), the comparison of overall survival favoured zanubrutinib, but was not statistically significant (restricted mean survival time: -1.59; 95% CI: -3.66, 0.48). After MAIC adjustment for 8 prognostic variables, the difference in overall survival favoured zanubrutinib, but remained not statistically significant (restricted mean survival time: -0.95; 95% CI: -3.69, 1.78). A similar result was seen after adjustment for only 5 prognostic variables (restricted mean survival time: -1.31; 95% CI: -3.98, 1.36).

6.50 The results of the MAICs were considered uncertain due to the limited number of prognostic and treatment effect modifier variables included for matching, limited documentation regarding the methodology used, the relative immaturity of data for the SEQUOIA trial used in the analysis, and the very low effective sample size after matching. Additionally, the submission did not propose non-inferiority margins for progression-free survival or overall survival. The lack of a statistically significant difference may not be sufficient to establish non-inferiority, as the 95% confidence intervals may include clinically important differences. As noted above, the resubmission argued that there are no accepted non-inferiority margins for these outcomes, and that a similar approach was accepted by the PBAC in the consideration of zanubrutinib at the March 2023 PBAC meeting.

Outcomes associated with ibrutinib retreatment

6.51 To support the request to allow patients who experience disease progression following treatment with ibrutinib + venetoclax to receive retreatment with ibrutinib monotherapy, the resubmission presented updated data on outcomes among patients who received post-progression retreatment with ibrutinib in the CAPTIVATE study. Data corresponding to a median follow-up of 38.7 months were presented in the November 2022 submission. The resubmission included additional data based on the most recent data cut for the CAPTIVATE study (median follow-up 55.7 months).

6.52 Of the 202 patients treated with ibrutinib + venetoclax in either the fixed duration cohort (n=159) or the MRD cohort (n=43), 53 had experienced progressive disease, with a median time to disease progression of 3.2 years (range: 1.0-5.5). Twenty-two of the patients who experienced disease progression received retreatment with ibrutinib monotherapy. With a median time on ibrutinib retreatment of 16.6 months (range: 0-45.0), the overall response rate in 21 evaluable patients was 86%, with best response of complete response in 1 patient, partial response in 17 patients, partial response with lymphocytosis in 1 patient, stable disease in 1 patient, and progressive disease in 1 patient. The resubmission stated that an additional 6 patients have started retreatment with ibrutinib + venetoclax, 7 patients have initiated other subsequent therapies, and 18 patients have received no subsequent treatment. The resubmission

argued that these data support that patients continue to respond with BTK inhibitor therapy after fixed duration ibrutinib + venetoclax, and in particular respond to ibrutinib monotherapy after having had fixed duration ibrutinib + venetoclax.

6.53 The resubmission stated that, based on available data, few patients who received fixed duration treatment with ibrutinib + venetoclax in the GLOW trial have so far received second-line therapy. Based on a median follow-up of 55 months in the ibrutinib + venetoclax arm, 4 patients (3.8%) received ibrutinib monotherapy as subsequent therapy as part of the study. The best response was complete response for 1 patient, partial response for two patients (one patients had not yet had a disease assessment).

6.54 The ESC considered that the data to support retreatment following ibrutinib + venetoclax was limited and noted there are alternative BTK inhibitor therapies available for patients who relapse or experience refractory disease following first-line treatment with ibrutinib.

Comparative harms

6.55 Table 11 presents a summary of safety outcomes for the GLOW, CAPTIVATE, CLL-14 and SEQUOIA trials at the time of the primary analysis for each trial.

Table 11: Comparison of adverse events for the GLOW, CAPTIVATE, CLL-14 and SEQUOIA trials

	GLOW		CAPTI-VATE	CLL-14		SEQUOIA		
	IBR + VEN	CHL + OBI	IBR + VEN	VEN + OBI	CHL + OBI	ZAN	BEN + RIT	ZAN (del 17p)
	N=106	N=105	N=159	N=212	N=214	N=240	N=227	N=111
Median follow-up, months (range)	27.7 (1.7-32.8)	27.9 (5.1-33.8)	27.9 (0.8-33.2)	28.1 (0.0-35.9)		26.4 (0.3-42.2)	25.9 (0.0-38.9)	30.5 (5.0-39.1)
Adverse event category, n %								
Any AE	105 (99.1)	99 (94.3)	158 (99.4)	200 (94.3)	213 (99.5)	224 (93.3)	218 (96.0)	109 (98.2)
Grade ≥3 AE[a]	80 (75.5)	73 (69.5)	99 (62.3)	167 (78.8)	164 (76.6)	126 (52.5)	169 (74.4)	61 (55.0)
SAE	49 (46.2)	29 (27.6)	36 (22.6)	104 (49.1)	90 (42.1)	88 (36.7)	113 (49.8)	45 (40.5)
Treatment-related SAE	26 (24.5)	20 (19.0)	21 (13.2)	NR	NR	NR	NR	NR
AE leading to death	7 (6.6)	2 (1.9)	1 (0.6)	16 (7.5)[b]	8 (3.7)[c]	11 (4.6)	12 (5.3)	3 (2.7)
Discontinue due to AE[d]	22 (20.8)	8 (7.6)	8 (5.0)	34 (16.0)	33 (15.4)	20 (8.3)	31 (13.7)	6 (5.4)
Dose reduction due to AE[d]	28 (26.4)	22 (21.0)	33 (20.8)	NR	NR	NR	NR	NR
Treatment-related AE	89 (84.0)	97 (92.4)	NR	NR	NR	NR	NR	NR

Source: Table 17, p85 of the GLOW clinical study report (primary analysis); Table 14.3.1.1.1, pp672-673 of the CAPTIVATE clinical study report (primary analysis); Table 2, pp2232-2233; p2230; p2234 of Fischer et al. (2019); Table S6, p50; Table S7, p51 of Fischer et al. (2019) supplementary appendix; p1038 of Tam et al. (2022); Table S7 and Table S8 of Tam et al. (2022) supplementary appendix.

Abbreviations: AE, adverse event; BEN, bendamustine; CHL, chlorambucil; IBR, ibrutinib; OBI, obinutuzumab; NR, not reported; RIT, rituximab; SAE, serious adverse event; VEN, venetoclax; ZAN, zanubrutinib.

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

[b] Includes 5 events during treatment and 11 events after completion of treatment.

[c] Includes 4 events during treatment and 4 events after completion of treatment.

[d] Discontinuation of any drug.

6.56 The most commonly reported adverse events (of any grade) in the ibrutinib + venetoclax arm of the GLOW trial were diarrhoea (50.9%), neutropenia (34.0%),

nausea (26.4%), anaemia (17.9%), rash (17.0%), urinary tract infection (16.0%), peripheral oedema (15.1%) and fatigue (15.1%). The most commonly reported Grade ≥3 adverse events were neutropenia (28.3%), diarrhoea (10.4%), neutrophil decreased (8.5%), hypertension (7.5%), atrial fibrillation (6.6%) and thrombocytopenia (5.7%).

6.57 Fatal treatment emergent adverse events occurred in 7 patients (6.6%) in the ibrutinib + venetoclax arm and 2 patients (1.9%) in the chlorambucil + obinutuzumab arm in the GLOW trial. Among the 7 treatment-emergent deaths in the ibrutinib + venetoclax arm, 4 occurred during lead-in treatment with ibrutinib. The fatal events included pneumonia, malignant neoplasm, and cardiac arrest. In one case, 3 fatal treatment emergent adverse events were reported (cardiac failure, pneumonia, and sinus node dysfunction). The remaining 3 deaths occurred during concomitant treatment with ibrutinib and venetoclax and included ischemic stroke (one patient) and sudden death (2 patients). In 6 of the 7 death cases, the investigator considered the fatal event was not related to study treatment. For the death case with 3 fatal treatment emergent adverse events, the events were reported as related to the study drug (ibrutinib).

6.58 The proportion of patients with atrial fibrillation was higher in the ibrutinib + venetoclax arm (14.2%) compared with the chlorambucil + obinutuzumab arm (1.9%). Grade 3 or 4 treatment-emergent adverse events of atrial fibrillation were reported in 7 patients (6.6%) in the ibrutinib + venetoclax arm and no patients in the chlorambucil + obinutuzumab arm. There were no fatal atrial fibrillation events.

6.59 Based on a naïve comparison with the venetoclax + obinutuzumab arm of the CLL-14 trial, a higher proportion of patients in the ibrutinib + venetoclax arm of the GLOW trial experienced Grade ≥3 (Grade 3-4 for the CLL-14 trial) diarrhoea (10.4% versus 4.2%) and neutrophil decrease (8.5% versus 4.2%), and a lower proportion experienced Grade ≥3 neutropenia (28.3% versus 52.8%), thrombocytopenia (5.7% versus 13.7%), anaemia (2.8% versus 8.0%), febrile neutropenia (1.9% versus 5.2%) and infusion-related reactions (0% versus 9.0%).

6.60 The resubmission argued that a high and broadly similar proportion of patients experienced an adverse event (of any grade), and a broadly similar proportion of patients experienced a Grade ≥3 adverse event, serious adverse event and adverse event leading to treatment discontinuation or death. The resubmission noted that infusion-related reactions occurred in almost half of venetoclax + obinutuzumab patients, whereas no patients treated with ibrutinib + venetoclax experienced an infusion-related reaction due to ibrutinib + venetoclax representing an all-oral treatment. The resubmission noted that atrial fibrillation was observed more frequently with ibrutinib + venetoclax. Comparisons were impacted by incomplete publishing of adverse event results for the comparator trials.

6.61 Based on a naïve comparison with the zanubrutinib arms of the SEQUOIA trial (non 17p deletion and 17p deletion arms, respectively), a higher proportion of patients in the ibrutinib + venetoclax arm of the GLOW trial experienced Grade ≥3 neutropenia (28.3% versus 9.2%/10.8%), diarrhoea (10.4% versus 0.8%/0.9%), neutrophil decrease

(8.5% versus 2.1%/4.5%) and thrombocytopenia (5.7% versus 1.7%/0.9%). The resubmission noted that ibrutinib + venetoclax was associated with numerically higher Grade ≥3 adverse events (75.5% versus 52.5%/55.0%), serious adverse events (46.2% versus 36.7%/40.5%), adverse events leading to treatment discontinuation (20.8% versus 8.3%/5.4%), and slightly more adverse events leading to death (6.6% versus 4.6%/2.7%) than zanubrutinib. However, the resubmission argued that the 26-month adverse event data from SEQUOIA is likely to have underestimated the true incidence of zanubrutinib adverse events, given that zanubrutinib treatment is ongoing for many patients.

6.62 The ESC considered that safety was broadly similar across the treatments. While it was noted that there were more AEs leading to death (Grade 5) in the ibrutinib + venetoclax arm (6.6%; and venetoclax + obinutuzumab arm [7.5%]) compared with the chlorambucil + obinutuzumab control arms for the GLOW and CLL-14 trials (1.9% and 3.7%), any increased toxicity was considered mostly attributable to venetoclax rather than ibrutinib (or obinutuzumab).

Benefits/harms

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

Clinical claim

6.64 The resubmission described fixed duration ibrutinib + venetoclax as non-inferior in terms of effectiveness, and non-inferior in terms of safety compared to fixed duration venetoclax + obinutuzumab. The ESC considered the claim of non-inferiority in terms of effectiveness was likely supported, but with a high degree of uncertainty.

6.65 While there were no statistically significant differences for any of the outcomes in the Bucher method indirect comparisons of ibrutinib + venetoclax versus venetoclax + obinutuzumab, there were differences in the chlorambucil treatment durations (median 5.5 months in GLOW versus 11.1 months in CLL-14) and progression-free survival outcomes (median progression-free survival of 23.0 months in GLOW versus 36.4 months in CLL-14) in the chlorambucil + obinutuzumab common reference arms which favoured ibrutinib + venetoclax.

6.66 Further, the ESC noted the results of the unanchored matching adjusted indirect comparisons (MAICs) of progression-free survival and overall survival for ibrutinib + venetoclax versus venetoclax + obinutuzumab and ibrutinib + venetoclax versus zanubrutinib used a limited number of variables for matching, and the differences in the trial populations across the studies resulted in a small effective sample size for the venetoclax + ibrutinib arms after matching. The pre-PBAC Response noted that the variables used within the MAICs were generally consistent with those included in MAICs considered by the PBAC in March 2023 and July 2023 when it recommended zanubrutinib and acalabrutinib, respectively, on a cost-minimisation basis against venetoclax and obinutuzumab.

6.67 The ESC considered that safety was broadly similar across the treatments. While it was noted that there were more AEs leading to death (Grade 5) in the ibrutinib + venetoclax arm (6.6%; and venetoclax + obinutuzumab arm [7.5%]) compared with the chlorambucil + obinutuzumab control arms for the GLOW and CLL-14 trials (1.9% and 3.7%), any increased toxicity was considered mostly attributable to venetoclax rather than ibrutinib (or obinutuzumab). However, the PBAC noted that 4 of the 7 deaths due to adverse events in the ibrutinib arm of the GLOW trial, and the single death in the CAPTIVATE study, occurred during the ibrutinib monotherapy lead-in period.

6.68 The PBAC considered that the clinical claim of non-inferior comparative effectiveness between ibrutinib + venetoclax and venetoclax + obinutuzumab was likely supported, but with some uncertainty given the indirect treatment comparisons presented.

6.69 The PBAC considered that the clinical claim of non-inferior safety between ibrutinib + venetoclax and venetoclax + obinutuzumab was reasonable, noting that the treatments have different adverse event profiles that should inform patient selection and monitoring, and that both treatments are associated with more Grade 5 AEs than other treatment options.

Economic analysis

6.70 The resubmission presented a cost-minimisation comparing treatment with fixed duration ibrutinib + venetoclax versus fixed duration venetoclax + obinutuzumab for patients with previously untreated CLL/SLL. Key components of the cost-minimisation approach are summarised in Table 12.

Table 12: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption	Comment
Therapeutic claim: effectiveness	The resubmission claimed that ibrutinib + venetoclax is non-inferior to venetoclax + obinutuzumab in terms of efficacy, based on the results of a Bucher method indirect comparison and an unanchored MAIC.	The results of the Bucher method indirect comparison did not appear to be appropriate due to differences in chlorambucil treatment durations and progression-free survival outcomes in the chlorambucil + obinutuzumab common reference arms. The results of the unanchored MAICs were considered highly uncertain due to the limited number of variables included for matching, and the very small effective sample size for the venetoclax + ibrutinib arm after matching.
Therapeutic claim: safety	The resubmission claimed that ibrutinib + venetoclax is non-inferior to venetoclax + obinutuzumab in terms of safety, based on the results of a naïve indirect comparison.	The claim of non-inferior safety was based on a naïve comparison between trials, which did not account for differences in patient characteristics between the trials.
Evidence base	Bucher method indirect comparison of ibrutinib + venetoclax (GLOW) versus venetoclax + obinutuzumab (CLL-14) using chlorambucil + obinutuzumab as the common reference. Unanchored matching adjusted indirect comparison of ibrutinib + venetoclax (GLOW) versus venetoclax + obinutuzumab (CLL-14).	The GLOW and CLL-14 trials recruited older/less fit patients whereas the proposed restriction also includes younger/fit patients.
Equi-effective doses	One initial and 8.67 continuing venetoclax scripts plus 7.355 obinutuzumab scripts are equivalent to 12.03 ibrutinib scripts plus 1.0 initial and 9.39 continuing venetoclax scripts	Treatment durations may be longer in clinical practice due to the broader proposed population that includes younger/fit patients. The resubmission inappropriately applied a 1-day reduction to the reported treatment durations for ibrutinib and venetoclax when deriving the script counts for ibrutinib + venetoclax.
Direct medicine costs	Venetoclax initial treatment script: $[redacted] [a] Venetoclax continuing treatment script: $[redacted] [a] Obinutuzumab: $[redacted] per script	Venetoclax costs were based on the current effective price for venetoclax for the treatment of relapsed/refractory CLL/SLL, which may not be applicable to the first-line treatment setting.
Other costs or cost offsets	Costs: baseline ECG cost, atrial fibrillation specialist monitoring costs, atrial fibrillation drug treatment costs. Cost offsets: obinutuzumab administration costs, obinutuzumab specialist visit costs and obinutuzumab premedication costs.	The ESC considered that costs associated with the management of atrial fibrillation may be underestimated given that atrial fibrillation may persist beyond the period of ibrutinib + venetoclax treatment, costs associated with atrial fibrillation hospitalisations were not included, and costs associated with other medications or procedures were not included.

Source: Table 3.1 of the resubmission.
Abbreviations: CLL, chronic lymphocytic leukemia; ECG, electrocardiogram; MAIC, matching adjusted indirect comparison; SLL, small lymphocytic lymphoma. [a] Estimated effective AEMP.

6.71 The resubmission noted that in the CLL-14 trial, the mean treatment duration for venetoclax was 288.1 days (Table 7, venetoclax PSD, July 2020 PBAC meeting). For the cost-minimisation, this was assumed to equate to 28 days of initial treatment (dose ramp-up phase) and 260.1 days of continuing treatment. The mean cumulative dose of obinutuzumab in the venetoclax + obinutuzumab arm of the CLL-14 trial was 7,355 mg (Table 7, venetoclax PSD, July 2020 PBAC meeting).

6.72 Recent updates to the CLL/SLL PBS restrictions allow use in a broader population of patients (i.e., treatment is no longer limited to patients with a CIRS score >6 or a creatinine clearance <70 mL/min). Younger patients with a lower burden of

comorbidities may have a longer treatment duration than those who are older and/or have comorbid conditions.

6.73 The resubmission noted that the dose intensities for venetoclax and obinutuzumab were not reported in the CLL-14 trial publications or in the venetoclax public summary documents. A dose intensity of 100% was assumed for venetoclax and obinutuzumab. The resubmission argued that this is consistent with the assumption used in the March 2023 submission for zanubrutinib in previously untreated CLL/SLL that received a positive recommendation (para 6.68, zanubrutinib PSD, March 2023 PBAC meeting).

6.74 Treatment durations for ibrutinib and venetoclax in the cost-minimisation were based on the treatment durations reported in the GLOW trial. At the primary analysis (median follow-up 27.7 months), the mean treatment durations for ibrutinib and venetoclax were 11.89 months and 10.21 months, respectively. The resubmission inappropriately applied a 1-day reduction to the reported treatment durations for ibrutinib and venetoclax when deriving the script counts for ibrutinib + venetoclax. A cost-minimised price for ibrutinib was also derived during the evaluation excluding the treatment duration adjustments.

6.75 The treatment duration among patients in the FD cohort of the CAPTIVATE study was longer than reported for the ibrutinib + venetoclax arm of the GLOW trial (mean treatment duration of 13.3 months for ibrutinib and 11.1 months for venetoclax at the primary analysis). Given that the requested population is not limited to older patients with comorbidities, the mean treatment duration for ibrutinib + venetoclax in clinical practice may be longer than assumed in the cost-minimisation. While a longer treatment duration would also be expected for venetoclax + obinutuzumab in the proposed population, the difference may be larger for ibrutinib + venetoclax due to the longer recommended treatment duration for ibrutinib + venetoclax (15 cycles) compared to venetoclax + obinutuzumab (12 cycles), and potentially lower use of ibrutinib + venetoclax in elderly/comorbid patients due to toxicity concerns. The ESC considered that while mean treatment duration in clinical practice may increase for both ibrutinib + venetoclax and venetoclax + obinutuzumab, that this would have minimal impact on the cost-minimised price.

6.76 The resubmission stated that dose intensity was not included in the cost-minimisation on the basis that the dose intensity in the CLL-14 trial has not been reported. The reported mean dose intensity at the primary analysis for the GLOW trial was 91.0% for ibrutinib and 89.9% for venetoclax. The reported mean dose intensity in the CAPTIVATE study was 95.4% for ibrutinib and 93.1% for venetoclax.

6.77 The following equi-effective doses were proposed:

- One initial and 8.67 continuing venetoclax scripts plus 7.355 obinutuzumab scripts are equivalent to 12.03 ibrutinib scripts plus 1.0 initial and 9.39 continuing venetoclax scripts.

6.78 After removal of the 1-day treatment duration adjustments applied to ibrutinib and venetoclax in the resubmission, the equi-effective doses were: one initial and 8.67 continuing venetoclax scripts plus 7.355 obinutuzumab scripts are equivalent to 12.06 ibrutinib scripts plus 1.0 initial and 9.43 continuing venetoclax scripts.

6.79 Table 13 summarises the costs and cost offsets included in the cost-minimisation approach.

Table 13: Costs and cost offsets included in the cost-minimisation

Characteristic	Cost per patient	Source
Ibrutinib + venetoclax		
Baseline ECG cost	$56.90	MBS item 11723 ($56.90), assuming 100% of patients treated with ibrutinib + venetoclax have a baseline ECG.
AF specialist monitoring costs	$40.79	MBS item 105 ($47.80), multiplied by the proportion experiencing AF of any grade in the GLOW trial (14.2%), assuming 6.01 visits (monthly visits for the first 3 months followed by 3-monthly visits, assuming a treatment duration based on 12.03 scripts).
AF medication costs	$57.64	Based on the published AEMP for apixaban 5 mg tablets (2735Y; $33.74 per 60 tablets), assuming 5 mg twice daily; multiplied by the average number of ibrutinib scripts per course (12.03) and the proportion experiencing AF of any grade in the GLOW trial (14.2%).
Venetoclax + obinutuzumab		
Baseline ECG cost	$0	Assumed that 0% of patients treated with venetoclax + obinutuzumab have a baseline ECG.
AF specialist monitoring costs	$1.25	MBS item 105 ($47.80), multiplied by the proportion serious adverse events of AF in the CLL-14 trial (0.5%), assuming 5.22 visits (monthly visits for the first 3 months followed by 3-monthly visits, assuming a treatment duration based on 9.67 scripts).
AF medication costs	$1.63	Based on the published AEMP for apixaban 5 mg tablets (2735Y; $33.74 per 60 tablets), assuming 5 mg twice daily; multiplied by the average number of ibrutinib scripts per course (12.03) and the proportion experiencing AF of any grade in the GLOW trial (14.2%).
Obinutuzumab IV infusion costs	$650.65	MBS Item 13950 ($118.30), assuming 5.5 infusions per patient per course. Assumed number of infusions based on the number of infusions included in the revised cost-minimisation of zanubrutinib versus venetoclax + obinutuzumab (para 6.73, zanubrutinib PSD, March 2023 PBAC meeting).
Obinutuzumab specialist visit costs	$461.73	MBS 116 ($83.95), assuming 5.5 specialist visits (i.e., one per infusion) per patient per course.
Obinutuzumab premedication costs	$8.31[a]	Based on the published AEMPs for paracetamol 500 mg tablets (PBS Item 1746X; $1.53 per pack of 100 tablets), dexamethasone 4 mg tablets (PBS Item 2507Y; $5.25 per pack of 30 tablets) and loratadine 10 mg tablets (PBS Item 4313B; $18.04 per pack of 30 tablets); assuming two paracetamol tablets per infusion ($1.53 ÷ 100 x 2 = $0.03), five dexamethasone tablets per infusion ($5.25 ÷ 30 x 5 = $0.88) and one loratadine tablet per infusion ($18.04 ÷ 30 = $0.60 per loratadine tablet); and assuming 5.5 infusions per course.

Source: Table 3.3, of the resubmission.
Abbreviations: AEMP, approved ex-manufacturer price; AF, atrial fibrillation; ECG, electrocardiogram.
[a] The cost per 30-pack of dexamethasone was incorrectly based on the price to pharmacy ($5.25) rather than the AEMP ($4.84). Updating based on the AEMP resulted in obinutuzumab premedication costs of $1.44 x 5.5 = $7.92.

6.80 Costs associated with the management of atrial fibrillation may be underestimated given that atrial fibrillation may persist beyond the period of ibrutinib + venetoclax treatment, costs associated with atrial fibrillation hospitalisations were not included, and costs associated with other medications (e.g., medicines to control heart rate) or

procedures (e.g., electrical cardioversion) were not included. The ESC considered that the cost-minimisation should be adjusted to accurately account for the cost of atrial fibrillation, which may persist beyond the period of ibrutinib + venetoclax treatment. The pre-PBAC Response defended the costing of AF in the CMA, stating that costing while on treatment only was consistent with previous ibrutinib submissions, and that the approach was conservative because all grades of AF were included in the costing, not just those Grade ≥3. The Response noted that this resulted in a cost per month per patient on treatment of AF of $12.91, which is higher than costs previously accepted by the PBAC of $12.06 for relapsed/refractory CLL and $7.17 for first-line CLL del17p.

6.81 The cost-minimisation assumed no impacts on CLL/SLL treatment utilisation and costs in the relapsed/refractory setting. However, choice of therapy in the first-line setting may impact later-line treatment options/utilisation.

6.82 Table 14 presents the derivation of the cost-minimised price for ibrutinib based on the estimated effective price of venetoclax. The cost-minimisation was performed at the AEMP level.

Table 14: Derivation of the cost-minimised price for ibrutinib

	Venetoclax + Obinutuzumab ($)	Ibrutinib + Venetoclax ($)
Treatment cost (venetoclax + obinutuzumab)		
VEN drug cost (AEMP) per course: ((1 x $[redacted]) + (8.67 x $[redacted]))[a]	[redacted]	-
OBI drug cost (AEMP) per course (7.355 x $[redacted])	[redacted]	-
OBI administration cost: MBS 13950 (5.5 x $118.30)	$650.65	-
OBI specialist visits (5.5 x $83.95)	$461.73	-
OBI premedication costs (5.5 x $1.51)	$8.31	-
AF medication cost (0.5% x 9.67 x $33.74)	$1.25	
AF specialist monitoring cost (0.5% x 5.22 x $47.80)	$1.63	
VEN + OBI total treatment costs per course	[redacted]	-
Cost-minimisation (ibrutinib + venetoclax)		
IBR + VEN total treatment cost per course	-	[redacted]
VEN drug cost (AEMP) per course ((1 x $[redacted]) + (9.39 x $[redacted]))[a]	-	[redacted]
AF medication cost (14.2% x 12.03 x $33.74)	-	$57.64
AF specialist monitoring cost (14.2% x 6.01 x $47.80)	-	$40.79
Baseline ECG cost (100% x $56.90)	-	$56.90
IBR cost per course ($[redacted] - $[redacted] - $57.64 - $40.79 - $56.90)	-	[redacted]
IBR cost (AEMP) per 140 mg or 420 mg script ($[redacted] ÷ 12.03 scripts)[b]	-	[redacted]
IBR cost (AEMP) per 280 mg script ($[redacted] ÷ 12.03 scripts x 2/3)		[redacted]
IBR cost (DPMQ) per 140 mg or 420 mg script[b]	-	[redacted]
IBR cost (DPMQ) per 280 mg script		[redacted]

Source: Section 3 economic analysis Excel workbook.

Abbreviations: AEMP, approved ex-manufacturer price; AF, atrial fibrillation; ECG, electrocardiogram; DPMQ, dispensed price for maximum quantity; IBR, ibrutinib; OBI, obinutuzumab; VEN, venetoclax.

[a] Based on the estimated effective AEMP for venetoclax initial and continuing scripts included in the resubmission.

[b] Proposed price per pack of 420 mg tablets (30 tablets per pack) and 140 mg capsules (90 capsules per pack).

6.83 Based on the cost minimisation, the resubmission estimated an AEMP per pack of 420 mg tablets (30 tablets per pack) and 140 mg capsules (90 capsules per pack) of $[redacted]; and an AEMP per pack of 280 mg tablets (30 tablets per pack) of $[redacted].

6.84 The resubmission presented the results of sensitivity analyses applying a 5% reduction to the estimated effective price of venetoclax (to reflect a 5% statutory price reduction for venetoclax expected in April 2024); assuming 7.355 obinutuzumab scripts rather than 5.5 scripts; and removing all additional costs and costs offsets (see Table 3.6 of the resubmission). The resulting impact on the ibrutinib AEMP was +0.4%, +1.2% and -3.0%, respectively.

6.85 Table 15 presents the results of additional sensitivity analyses conducted during the evaluation.

Table 15: Sensitivity analyses conducted during the evaluation

Analyses	AEMP[a] ($)	% change in AEMP
Resubmission base case		-
Removal of 1 day adjustment applied to mean treatment duration		-0.7%
Removal of 1 day adjustment applied to mean treatment duration and dexamethasone cost based on AEMP (rather than price to pharmacy)		-0.7%
Mean treatment duration for ibrutinib and venetoclax based on the CAPTIVATE study (13.3 months and 11.0 months, respectively)		-18.9%

Source: Constructed during the evaluation using the Section 3 cost-minimisation Excel workbook.
Abbreviations: AEMP, approved ex-manufacturer price.
[a] Analyses based on AEMP for 420 mg tablets (pack of 30) and 140 mg capsules (pack of 120).

Drug cost/patient/course

6.86 Table 16 presents a comparison of drug costs for ibrutinib + venetoclax and venetoclax + obinutuzumab included in the economic model and financial estimates.

Table 16: Drug cost per patient for ibrutinib + venetoclax and venetoclax + obinutuzumab

	Clinical trial[a]	Cost-minimisation	Financial estimates
Ibrutinib + venetoclax			
IBRUTINIB			
Cost per script (AEMP)	-	$	$
Compliance	Mean exposure: 11.89 months; 91.0% dose intensity	12.03 scripts	12.03 scripts
Cost per course	-	$	$
VENETOCLAX			
Cost per script (AEMP)	-	Starter pack: $ [b] Continuing pack: $ [b]	Starter pack: $ [b] Continuing pack: $ [b]
Compliance	Mean exposure: 10.21 months; 89.9% dose intensity	Starter pack: 1 Continuing pack: 9.39	Starter pack: 1 Continuing pack: 9.39
Cost per course	-	$	$
Total cost per course	-	**$**	**$**
Venetoclax + obinutuzumab			
VENETOCLAX			
Cost per script (AEMP)	-	Starter pack: $ [b] Continuing pack: $ [b]	Starter pack: $ [b] Continuing pack: $ [b]
Compliance	Starter pack: 1 Continuing pack: 8.67	Starter pack: 1 Continuing pack: 8.67	Starter pack: 1 Continuing pack: 8.67
Cost per course	-	$	$
OBINUTUZUMAB			
Cost per script (AEMP)	-	$	$
Compliance	7.355 scripts/course	7.355 scripts/course	7.355 scripts/course
Cost per course	-	$	$
Total cost per course	-	**$**	**$**

Source: Table 7, pp52-53 of the GLOW trial clinical study report (primary analysis); Section 3 economic analysis Excel workbook; Section 4 financial estimates Excel workbook.

Abbreviations: NE, not estimable.

[a] Based on the GLOW trial for ibrutinib + venetoclax and the CLL-14 trial for venetoclax + obinutuzumab.

[b] Estimated effective AEMP based on effective price of venetoclax in the relapsed/refractory setting.

Estimated PBS usage & financial implications

6.87 This submission was not considered by DUSC.

6.88 A comparison of the budget impact implications between the current resubmission and the December 2022 submission was not considered to be informative given the substantial changes in patient population, intervention, comparator and methodology for utilisation estimates between submissions.

6.89 The resubmission used a market share approach to estimate the utilisation and financial implications of listing ibrutinib + venetoclax on the PBS/RPBS for the first-line treatment of CLL/SLL. Key inputs relied on in the financial estimates are summarised in Table 17.

Table 17: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value applied and source	Comment
Treatment utilisation		
Obinutuzumab scripts (projected current market)	From [redacted][1] in Year 1 to [redacted][1] in Year 6. Based on PBS script data for obinutuzumab items used in combination with venetoclax between 2020 and 2022. Total script count extrapolated using the logarithmic trend line function in Excel.	Estimates do not account for the change in the listings of venetoclax and obinutuzumab in September 2023 which broadened the eligibility criteria for these therapies from unfit patients only to any patient requiring first-line treatment for CLL/SLL. However, the ESC previously noted that the expansion of the venetoclax with obinutuzumab listing was unlikely to substantially affect utilisation estimates (para 6.59, acalabrutinib PSD, July 2023 PBAC meeting). Estimates of utilisation between 2020 and 2022 may be affected by the COVID-19 pandemic and may not be representative of longer-term utilisation patterns. Additionally, venetoclax + obinutuzumab has only been subsidised under the PBS since December 2020 and market dynamics may change over time.
Venetoclax scripts (projected current market)	From [redacted][1] in Year 1 to [redacted][1] in Year 6. Based on PBS script data for venetoclax items used in combination with obinutuzumab between 2020 and 2022. Total script count extrapolated using the logarithmic trend line function in Excel. After extrapolation of the combined venetoclax scripts the resubmission disaggregated projected scripts assuming the distribution in 2022 between initial, 1st continuing and 2nd continuing scripts remains constant over time.	
Ibrutinib + venetoclax substitution rate	From 25% in Year 1 to 60% in Years 5-6. Estimates were assumed based on the expectation of a relatively high substitution rate as ibrutinib + venetoclax would be the only available all-oral, fixed duration treatment option.	The substitution rate appeared high given the other potential treatment options for first-line treatment of patients for CLL/SLL. In particular, the zanubrutinib PBAC submission assumed that zanubrutinib monotherapy would capture 40% of the venetoclax + obinutuzumab market (Table 14, zanubrutinib PSD, March 2023 PBAC meeting), while the acalabrutinib PBAC submission assumed that acalabrutinib with or without obinutuzumab would capture 30-50% of the venetoclax + obinutuzumab market (Table 19, acalabrutinib PSD, July 2023 PBAC meeting).
Ibrutinib + venetoclax script adjustment factors	- 3 initial ibrutinib scripts vs. 1 initial venetoclax script - 1.2 first continuing ibrutinib scripts vs. 1 first continuing venetoclax script - 0.83 second continuing ibrutinib scripts vs. 1 second continuing venetoclax script - 1.41 venetoclax scripts vs. 1 obinutuzumab script Based on the dosing relativities used in the cost-minimisation assuming that patients are fully adherent to recommended dosing schedules and the differences in treatment duration are due to non-persistence. The script estimates assumed that the full course of treatment is administered in a single year (the recommended treatment duration for ibrutinib + venetoclax is 15 months and the recommended treatment duration for venetoclax + obinutuzumab is 12 months).	The resubmission did not adequately justify the mapping of individual components of the new treatment regimen to individual components of the current treatment regimen (new ibrutinib mapped to current venetoclax, new venetoclax mapped to current obinutuzumab). The assumption that patients are fully adherent to the dosing schedule of treatment was unlikely to be representative of clinical practice. The assumption that all treatments would be administered within a year appeared to be a reasonable simplifying assumption.

Source: Section 4.1 of the resubmission
Abbreviations: CLL, chronic lymphocytic leukaemia; ESC, Economic Sub-Committee; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; PSD, Public Summary Document; SLL, small lymphocytic lymphoma.
The redacted values correspond to the following ranges:
[1] 5,000 to < 10,000

6.90 The estimated utilisation and financial implications (using the estimated effective DPMQ) of a PBS listing of ibrutinib + venetoclax for the first-line treatment of CLL/SLL is summarised in Table 18.

Table 18: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of ibrutinib scripts dispensed	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]
Number of venetoclax scripts dispensed	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]
Cost to the PBS/RPBS (less copayments)						
Cost to PBS/RPBS for ibrutinib + venetoclax	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][5]	[redacted][5]	[redacted][6]
Cost-offsets for reduced use of venetoclax + obinutuzumab	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
Costs for increased use of apixaban for atrial fibrillation	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]
Net cost to PBS/RPBS	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]
Cost to the MBS						
Costs for increased monitoring associated with atrial fibrillation	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]
Net financial implications						
Net cost to PBS/RPBS/MBS	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]

Source: Table 4.4; Table 4.9, Table 4.15, Table 4.15; Table 4.20 of the resubmission
Abbreviations: MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme
The redacted values correspond to the following ranges:
[1] 500 to < 5,000
[2] 5,000 to < 10,000
[3] $10 million to < $20 million
[4] $20 million to < $30 million
[5] $30 million to < $40 million
[6] $40 million to < $50 million
[7] net cost saving
[8] $0 to < $10 million

6.91 The estimated net cost to the PBS/RPBS was $0 to < $10 million in Year 1, increasing to $0 to < $10 million in Year 6, with a cumulative total of $0 to < $10 million over the first 6 years of listing. The estimated costs from changes to the use of MBS services was $0 to < $10 million in Year 1, increasing to $0 to < $10 million in Year 6, with a cumulative total of $0 to < $10 million over the first 6 years of listing.

6.92 The estimated cumulative net cost to the PBS/RPBS/MBS was $0 to < $10 million over the first 6 years of listing.

6.93 The proposed listing of ibrutinib + venetoclax was associated with an overall net cost primarily due to the exclusion of some cost-offsets from the budget impact analyses

which were included in the cost-minimisation (i.e., cost offsets for obinutuzumab premedication, administration and monitoring).

Quality Use of Medicines

6.94 The resubmission stated that the sponsor will provide educational support to patients, doctors, pharmacists and other healthcare professionals, including education regarding the use of ibrutinib as a fixed duration therapy rather than as an ongoing therapy for existing indications, and additional education on the management of atrial fibrillation associated with ibrutinib treatment.

Financial Management – Risk Sharing Arrangements

6.95 The ESC noted that while the resubmission did not propose a Risk Sharing Arrangement (RSA), the sponsor stated they would be amenable to an arrangement if deemed appropriate by the PBAC. The resubmission noted that the sponsor is aware that the current listing of venetoclax as a first-line therapy for CLL/SLL is subject to a RSA.

6.96 It is unclear whether the sponsor for venetoclax would be willing to agree to the proposed restriction and any consequent changes to existing RSAs (in the first-line and/or subsequent-line setting).

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

7 PBAC Outcome

7.1 The PBAC recommended extending the listing of ibrutinib, to include use in combination with venetoclax (IBR+VEN), for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL). The PBAC's recommendation for listing was based on its assessment that the cost-effectiveness of IBR+VEN would be acceptable if it were cost-minimised against venetoclax in combination with obinutuzumab (VEN+OBI). In making its recommendation, the PBAC also considered the clinical need and the equity of access advantages associated with an all-oral therapy.

7.2 The PBAC noted and welcomed the input from 73 respondents (including 64 individuals), with the main comment being that, compared with VEN+OBI (where OBI requires an IV infusion), the availability of an all-oral combination of IBR+VEN would provide improved patient access and convenience given there is no need for in-hospital/clinic treatment or time away from work for infusions, and more equitable access for rural and remote patients.

7.3 The PBAC considered that the nominated main comparator of VEN+OBI was appropriate. The PBAC noted that zanubrutinib had been included as a supplementary comparator.

7.4 The PBAC noted this was the second submission for IBR for this indication, and that this resubmission had addressed PBAC concerns raised in their assessment of the

previous submission at the December 2022 intracycle meeting. Changes included removing the requirement for patients to be considered fit for treatment with fludarabine based chemoimmunotherapy and, based on the expanded patient population, changing the comparator from fixed duration fludarabine + cyclophosphamide to VEN+OBI (main comparator) and zanubrutinib (supplementary comparator).

7.5 The PBAC noted that as there were no head-to-head trials available comparing IBR+VEN and VEN+OBI, the submission presented indirect comparisons utilising data from the following randomised trials: GLOW (IBR+VEN versus chlorambucil versus OBI [CHL+OBI]), CLL-14 (VEN+OBI versus CHL+OBI) and SEQUOIA (zanubrutinib versus bendamustine + rituximab). An additional single-arm IBR+VEN study (CAPTIVATE) was also included because it provided data in a younger (more "fit") patient population.

7.6 The PBAC noted that the resubmission had presented an anchored Bucher indirect treatment comparison (ITC) using CHL+OBI as a common comparator, which showed there was no statistically significant difference between IBR+VEN and VEN+OBI in terms of progression free survival (PFS; HR 0.69; 95% CI: 0.42, 1.16) and overall survival (OS; HR 0.54; 95% CI: 0.26, 1.13). The PBAC noted lower PFS and OS in the CHL+OBI arm of GLOW versus the CHL+OBI arm of CLL-14 and that these differences may be due to the substantially lower CHL dosing in the GLOW trial. The PBAC noted that in previous instances when CHL has been used as a common comparator that variations in CHL dosing has not been considered a significant issue (Ofatumumab, November 2014; Ibrutinib, November 2017).

7.7 The PBAC noted that the resubmission also presented an unanchored matching adjusted indirect comparison (MAIC) utilising data from the IBR+VEN and VEN+OBI arms only of the GLOW and CLL-14 trials. The PBAC considered the results uncertain due to the unanchored nature of the comparison, the limited number of prognostic and treatment effect modifier variables available for matching, limited documentation regarding the methodology used, differences in trial eligibility and the low effective sample size after matching (e.g., n=46 out of 106 patients in GLOW).

7.8 The PBAC noted that the rate of Grade ≥3 adverse events (AEs) and serious AEs (SAEs) were similar between IBR+VEN and VEN+OBI: 75.5% versus 78.8% for Grade ≥3 AEs, and 46.2% versus 49.1% for SAEs. Grade 5 AEs (causing death) were higher for IBR+VEN (6.6%) and VEN+OBI (7.5%) compared with CHL+OBI (1.9% and 3.7% in the GLOW and CLL-14 trials), which the ESC suggested may be more likely due to the VEN component. However, the PBAC noted that 4 of the 7 deaths due to AEs in the IBR arm of the GLOW trial, and the single death in the CAPTIVATE study, occurred during the IBR monotherapy lead-in period.

7.9 The PBAC considered that the clinical claim of non-inferior effectiveness between IBR+VEN and VEN+OBI is likely supported, but with some uncertainty due to differences in the CHL dosing and results for the common arm in the anchored ITC, as well as issues around the selection of variables for the unanchored MAIC, and the lack

of transparency around the methodology used.

7.10 The PBAC considered that the safety of IBR+VEN and VEN+OBI is broadly similar, and that the two treatments have different AE profiles (e.g., the increased risk of atrial fibrillation [AF] seen with IBR+VEN) that should inform patient selection and monitoring. While both IBR+VEN and VEN+OBI were associated with more Grade 5 AEs than CHL+OBI, early deaths were not as common in the CAPTIVATE IBR+VEN single-arm study that included a younger, fitter patient group.

7.11 The PBAC noted that the resubmission presented a cost-minimisation approach (CMA) of IBR+VEN compared to VEN+OBI. The PBAC noted this was in line with its advice from the December 2022 meeting and considered this was appropriate and consistent with the claim of non-inferior efficacy and safety.

7.12 The PBAC noted that the equi-effective doses were as follows: 1.0 initial and 8.67 continuing VEN scripts plus 7.355 OBI scripts are equivalent to 12.06 IBR scripts plus 1.0 initial and 9.43 continuing VEN scripts.

7.13 The PBAC noted that the mean treatment duration for IBR+VEN was based on the GLOW trial, which specifically included older or more comorbid patients (≥65 years or 18-64 years and CIRS score >6 or CrCl <70 ml/min), while the requested population was not limited by age (other than ≥18 years) or comorbidity, and as such, treatment duration in clinical practice may be longer than assumed in the CMA. However, the PBAC noted that this broadening of the population also applied to the listing of VEN+OBI, which was based on the CLL-14 trial and which also included an older, more comorbid population (CIRS score >6 or CrCl <70 ml/min). Thus, the PBAC considered that this was likely to have minimal effect on the cost-minimised price.

7.14 The PBAC noted that the CMA should result in the cost of IBR+VEN being no more than the cost of VEN+OBI, based on the effective approved ex-manufacturer prices and accurately accounting for differences in AF (i.e., as calculated in Table 14, with an incremental cost of $[redacted]).

7.15 The PBAC noted that the resubmission's utilisation and financial impact estimates for IBR+VEN resulted in a small overall net PBS/RPBS/MBS cost, primarily due to the exclusion of some cost offsets that were included in the cost-minimisation, including the IV administration cost for obinutuzumab. Noting that IBR+VEN would substitute for VEN+OBI, the PBAC considered that the listing of IBR+VEN should be overall approximately cost neutral.

7.16 The PBAC noted that a Risk Sharing Arrangement (RSA) consisting of subsidisation caps is in place for VEN and that as VEN+IBR will replace VEN+OBI an increase in the use of VEN is not expected and thus no increase to the financial caps would be required to account for the new listing. Additionally, noting that RSAs are in place for both zanubrutinib and for acalabrutinib for the first-line treatment of CLL/SLL, the Committee considered that a RSA for ibrutinib may also be appropriate.

7.17 The PBAC noted the request for a grandfather restriction due to the planned early

access to IBR+VEN 3 months prior to PBS listing and considered this was appropriate.

7.18 The PBAC agreed with the ESC that the evidence for retreatment with ibrutinib is immature and that patients currently have the option of treatment with other BTK inhibitor therapies that are available in the relapsed/refractory setting, noting that in most cases, the physician will choose another agent due to the better safety profiles of the alternative therapies.

7.19 The PBAC advised that flow-on changes would be required to the current venetoclax listing to allow its use in combination with ibrutinib in CLL/SLL, and noted that the restrictions suggested in the submission would provide enough tablets for the initial 5-week ramp-up schedule added to ibrutinib therapy at Week 4 (with dosing increasing weekly from 20 mg to 400 mg), followed by 12 30-day cycles at 400 mg.

7.20 The PBAC considered the restriction to be complex due to the potential flow on changes to the venetoclax listing.

7.21 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because IBR+VEN is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over VEN+OBI, or not expected to address a high and urgent unmet clinical need given the presence of alternative therapies, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines - Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

7.22 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 new indication as follows:

INITIAL TREATMENT (CYCLES 1 TO 3 INCLUSIVE)

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
IBRUTINIB					
ibrutinib 140 mg capsule, 90	NEW	1	90	2	Imbruvica
ibrutinib 280 mg tablet, 30	NEW	1	30	2	Imbruvica
ibrutinib 420 mg tablet, 30	NEW	1	30	2	Imbruvica
Restriction Summary [new] / Treatment of Concept: [new]					
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: ☒Medical Practitioners				
	Restriction type: ☒ Authority Required (telephone/electronic via PBS Authorities system)				
	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. Blood vol. 131, 25 (2018): 2745-2760.
		Administrative Advice: A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.
		Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
		Treatment Phase: Initial treatment in first-line therapy (treatment cycles 1 to 3 inclusive)
		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 treatment of CLL/SLL,
		AND
		Clinical criteria:
		The treatment must only be prescribed for a patient 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 in combination with venetoclax (refer to Product Information for timing of ibrutinib and venetoclax doses).
		Prescriber Instruction: There are more ibrutinib capsules (or tablets) in a pack than is required for the completion of a treatment cycle. The patient must not discard any remaining capsules (or tablets) after the completion of any treatment cycle as these capsules (or tablets) will be required for the doses in the final treatment cycle (i.e. treatment cycle 15).

FIRST CONTINUING (CYCLES 4 TO 9 INCLUSIVE)

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
IBRUTINIB					
ibrutinib 140 mg capsule, 90	NEW	1	90	5	Imbruvica
ibrutinib 280 mg tablet, 30	NEW	1	30	5	Imbruvica
ibrutinib 420 mg tablet, 30	NEW	1	30	5	Imbruvica
Restriction Summary [new] / Treatment of Concept: [new]					
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: ☒Medical Practitioners				
	Restriction type: ☒ Authority Required (telephone/electronic via PBS Authorities system)				

	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: A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.
	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.
	Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
	Treatment Phase: First continuing treatment (treatment cycles 4 to 9 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 venetoclax (refer to Product Information for timing of ibrutinib and venetoclax doses)
	AND
	Clinical criteria:
	The treatment must cease upon disease progression.
	Prescriber Instruction: There are more ibrutinib capsules (or tablets) in a pack than is required for the completion of a treatment cycle. The patient must not discard any remaining capsules (or tablets) after the completion of any treatment cycle as these capsules (or tablets) will be required for the doses in the final treatment cycle (i.e. treatment cycle 15).

GRANDFATHER TREATMENT - TRANSITIONING FROM NON-PBS TO PBS-SUBSIDISED SUPPLY OF FIRST-LINE THERAPY

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
IBRUTINIB					
ibrutinib 140 mg capsule, 90	NEW	1	90	5	Imbruvica
ibrutinib 280 mg tablet, 30	NEW	1	30	5	Imbruvica
ibrutinib 420 mg tablet, 30	NEW	1	30	5	Imbruvica

Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒ Authority Required (telephone/electronic via PBS Authorities system)
	Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
	Treatment Phase: Grandfather treatment - Transitioning from non-PBS to PBS-subsidised supply of first-line therapy
	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: A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.
		Administrative Advice: 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: 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. Blood vol. 131, 25 (2018): 2745-2760.
		Clinical criteria
		Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to [PBS listing date XXX]
		AND
		Clinical criteria
		Patient must not have developed disease progression while receiving treatment with this drug for this condition
		Clinical criteria:
		The condition must have been 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 treatment of CLL/SLL at the time of receiving non-PBS-subsidised treatment with this drug for this condition,
		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 in combination with venetoclax (refer to product Information for timing of ibrutinib and venetoclax doses).
		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: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria
		Prescribing Instruction: A patient may qualify for PBS-subsidised treatment under this restriction once only.
		Prescribing Instruction: For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the next relevant treatment phase.
		Prescriber Instruction: There are more ibrutinib capsules (or tablets) in a pack than is required for the completion of a treatment cycle. The patient must not discard any remaining capsules (or tablets) after the completion of any treatment

	cycle as these capsules (or tablets) will be required for the doses in the final treatment cycle (i.e. treatment cycle 15).

SECOND & FINAL CONTINUING (CYCLES 10 TO 15 INCLUSIVE)

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
IBRUTINIB					
ibrutinib 140 mg capsule, 90	NEW	1	90	4	Imbruvica
ibrutinib 280 mg tablet, 30	NEW	1	30	4	Imbruvica
ibrutinib 420 mg tablet, 30	NEW	1	30	4	Imbruvica

Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒ Authority Required (telephone/electronic via PBS Authorities system)
	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: A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.
	Administrative Advice: 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.
	Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
	Treatment Phase: Second and final continuing treatment (treatment cycles 10 to 15 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 venetoclax (refer to Product Information for timing of ibrutinib and venetoclax doses)
	AND
	Clinical criteria:
	The treatment must cease upon disease progression; OR.
	The treatment must cease upon completion of 15 cycles of treatment with this drug for this condition, whichever comes first.
	Prescriber Instruction: There are more ibrutinib capsules (or tablets) in a pack than is required for the completion of a treatment cycle. The patient must not discard any remaining capsules (or tablets) after the completion of any treatment cycle as these capsules (or tablets) will be required for the doses in the final treatment cycle (i.e. treatment cycle 15).

8.2 The following flow-on changes will be required to the venetoclax restrictions. Add the following new restrictions as follows:

INITIAL TREATMENT IN FIRST-LINE THERAPY – DOSE TITRATION (WEEKS 1 TO 4 OF A 5-WEEK RAMP-UP SCHEDULE)

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
VENETOCLAX					
venetoclax 10 mg tablet [14] (&) venetoclax 50 mg tablet [7] (&) venetoclax 100 mg tablet [7] (&) venetoclax 100 mg tablet [14], 1 pack	NEW	1	1	0	Venclexta

Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒ Authority Required (telephone/electronic via PBS Authorities system)
	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. Blood vol. 131, 25 (2018): 2745-2760.
	Administrative Advice: A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.
	Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
	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 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 treatment of CLL/SLL,
	AND
	Clinical criteria:
	The treatment must only be prescribed for a patient 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 in combination with ibrutinib (refer to Product Information for timing of ibrutinib and venetoclax doses).

FIRST CONTINUING TREATMENT (TREATMENT CYCLES 4 TO 8 INCLUSIVE) OF FIRST-LINE THERAPY

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
VENETOCLAX					
Venetoclax 100 mg tablet, 120	NEW	1	120	4	Venclexta
Restriction Summary [new] / Treatment of Concept: [new]					
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: ☒ Medical Practitioners				
	Restriction type: ☒ Authority Required (telephone/electronic via PBS Authorities system)				
	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.				
	Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)				
	Treatment Phase: First continuing treatment (treatment cycles 4 to 8 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 ibrutinib (refer to Product Information for timing of ibrutinib and venetoclax doses)				
	AND				
	Clinical criteria:				
	The treatment must cease upon disease progression.				

SECOND AND FINAL CONTINUING TREATMENT PRESCRIPTION (TREATMENT CYCLES 9 TO 15 INCLUSIVE) OF FIRST-LINE THERAPY

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
VENETOCLAX					
Venetoclax 100 mg tablet, 120	NEW	1	120	5	Venclexta
Restriction Summary [new] / Treatment of Concept: [new]					
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: ☒ Medical Practitioners				
	Restriction type: ☒ Authority Required (telephone/electronic via PBS Authorities system)				
	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.
		Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
		Treatment Phase: Second and final continuing treatment prescription (treatment cycles 9 to 15 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 ibrutinib (refer to Product Information for timing of ibrutinib and venetoclax doses)
		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.

8.3 The following flow-on changes will also be required to the venetoclax restrictions 12188L and 12199C as follows:

- concept ID 11532 "Administrative Advice: A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime" will need to be added to restriction 12188L, and
- concept ID 26595 will need to be added to restriction 12199C, i.e., "the treatment must be in combination with obinutuzumab (refer to Product Information for timing of obinutuzumab and venetoclax doses)".

This restriction may be subject to further review. Should there be any changes made to the restrictions 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.