6.05 IBRUTINIB, Capsule 140 mg, Imbruvica®, JANSSEN-CILAG PTY LTD.

1 Purpose of submission

1.1 The Category 2 submission requested a General Schedule Authority Required (Written) listing for ibrutinib, for use in combination with venetoclax, for the treatment of previously untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL).

1.2 The requested population includes patients who would be considered fit for treatment with fludarabine-based chemoimmunotherapy. Fit patients include those who are typically younger with good organ function and fewer comorbidities.

1.3 Listing was requested on the basis of a cost-effectiveness/cost-utility analysis versus chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

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 (15 cycles in total, fixed duration therapy) per the following regimen: - Oral ibrutinib: 420 mg once daily for 15 28-day cycles. - Oral venetoclax: 5-week dose ramp-up followed by 400 mg daily starting at cycle 4 and continued for 12 cycles.
Comparator	Fludarabine, cyclophosphamide, and rituximab (FCR; 6 cycles in total, fixed duration therapy) per the following regimen: - IV fludarabine: 25 mg/m^2 on days 1 through 3 of cycles 1 to 6 - IV cyclophosphamide: 250 mg/m^2 on days 1 through 3 of cycles 1 to 6 - IV rituximab: 50 mg/m^2 on day 1 of cycle 1; 325 mg/m^2 on day 2 of cycle 1; and 500 mg/m^2 on day 1 of cycles 2 through 6.
Outcomes	Progression-free survival, overall survival, overall response rate, complete response rate, MRD negativity, adverse events.
Clinical claim	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, p17 of the submission.
Abbreviations: CLL/SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; FCR, fludarabine, cyclophosphamide, and rituximab; IV, intravenous; MRD, minimal residual disease.

2 Background

Previous PBAC consideration

2.1 In November 2019, the PBAC recommended ibrutinib monotherapy for the first-line treatment of CLL/SLL in patients with deletion 17p (del17p), which may overlap with a portion of the population requested in the current submission which is agnostic to

del17p. The recommendation was on the basis of superior comparative effectiveness (in terms of PFS) versus obinutuzumab + chlorambucil. The current submission stated that the sponsor was, at that time, unable to proceed to PBS listing due to conditions imposed with the recommendation.

Registration status

2.2 The submission was made under the TGA/PBAC parallel process. At the time of evaluation for PBAC consideration, the first-round clinical evaluation report was available. The TGA delegate's overview was finalised on 25 November 2022.

2.3 The proposed change to the current TGA indication for ibrutinib + venetoclax (in bold) was initially:

> Ibrutinib as a single agent or in combination with rituximab or obinutuzumab **or venetoclax** is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia/small lymphocytic leukemia (CLL/SLL). Can be used in patients with deletion 17p.

2.4 During the TGA evaluation, the sponsor later proposed amending the initially proposed TGA indication from "Can be used in patients with deletion 17p" to "Can be used in patients with deletion 17p or clinically significant TP53 variant".

2.5 The basis of the TGA evaluation was the GLOW trial, a randomised, open-label, Phase 3 study of older patients (aged 65 years or older) and/or those with comorbidities, comparing ibrutinib + venetoclax with chlorambucil + obinutuzumab. The fixed-duration (FD) cohort of CAPTIVATE, the key evidence in this PBAC submission, was included as supportive evidence in the TGA evaluation. The TGA clinical evaluator raised concerns around the number of patients who died due to cardiac failure and arrhythmias that may have been contributed to by ibrutinib in the GLOW trial, particularly in a first-line therapy. The TGA evaluator noted that the current advice in the product information does not adequately convey this risk, and it should be amended to note that patients with pre-existing cardiac risk factors should consider other treatment options.

2.6 The Delegate's Overview stated, "While a decision is yet to be made, at this stage I may be inclined to approve the registration of the product."

- The Delegate sought advice from the ACM which included: "The Overall Survival data [referring to the GLOW trial] are currently immature. Given the evidence to date, and considering the disease context, please advise on whether these data are sufficient to draw conclusions about the benefits of the ibrutinib and venetoclax in the proposed indication".
- The Delegate also concluded "A concern with this submission is the safety of the regimen. There is an increasing strength in the signal for cardiovascular risk for ibrutinib, a known risk with this medicine. While the evidence to date

is promising, long term data are still awaited to understand the durability of effect for responders to the fixed duration course of treatment, and whether there is ultimately an overall survival benefit for this regimen".

The Delegate's Overview also noted that fatal cardiac adverse events had occurred with ibrutinib and that the sponsor proposed a more conservative dose modification approach might be required to reduce risk.

2.7 The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended ibrutinib (with changes to the existing indication in bold) as a single agent or in combination with rituximab or obinutuzumab or **venetoclax** for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) in June 2022.

2.8 In its response to the TGA Clinical Evaluation Report, the sponsor noted that [redacted].

3 Requested listing

3.1 The requested listing is provided below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

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
Restriction Summary / Treatment of Concept:					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: ☒Medical Practitioners					
Restriction type: ☒ Authority Required (telephone/electronic via PBS Authorities system)~~– non-immediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart; requires at least one concept ID to be marked as 'FULL' for full assessment by Services Australia)~~					
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 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).*					
Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)					
Treatment Phase: Initial treatment in first-line therapy *(treatment cycles 1 to 3 inclusive)* ~~– 3-cycle lead-in~~					
Clinical criteria:					

The condition must be untreated
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition
AND
Clinical criteria:
Patient must have a cumulative illness rating scale (CIRS) score of less than or equal to 6 (excluding CLL-induced illness or organ damage)
AND
Clinical criteria:
Patient must have a creatinine clearance greater than or equal to 70 mL/min
AND
Clinical criteria:
Patient must have a WHO performance status of 0 or 1
Prescriber Instruction: *There are more ibrutinib capsules in a pack than is required for the completion of a treatment cycle. The patient must not discard any remaining capsules after the completion of any treatment cycle as these capsules will be required for the doses in the final treatment cycle (i.e. treatment cycle 15).*

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

Restriction Summary / Treatment of Concept:
Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒ Authority Required (telephone/electronic via PBS Authorities system) ~~non-immediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart; requires at least one concept ID to be marked as 'FULL' for full assessment by Services Australia)~~
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
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Administrative Advice: *A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.*
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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 in a pack than is required for the completion of a treatment cycle. The patient must not discard any remaining capsules after the completion of any treatment cycle as these capsules will be required for the doses in the final treatment cycle (i.e. treatment cycle 15).*
Restriction Summary / Treatment of Concept:
Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒ Authority Required (telephone/electronic via PBS Authorities system)~~– non-immediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart; requires at least one concept ID to be marked as 'FULL' for full assessment by Services Australia)~~
Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply *of first-line therapy – Grandfather arrangements*
Clinical criteria:
The treatment must be in combination with venetoclax (refer to Product Information for timing of ibrutinib and venetoclax doses)
AND
Clinical criteria:
Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to [listing date]~~,~~
AND
Clinical criteria:
~~Patient must have met all initial treatment PBS-eligibility criteria applying to a non-grandfathered patient prior to having commenced treatment with this drug, which are:~~
The condition must *have* be*en* untreated *prior to initiating non-PBS-subsidised treatment with this drug for this condition.*
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition
AND
Clinical criteria:
Patient must have *had* a cumulative illness rating scale (CIRS) score of less than or equal to 6 (excluding CLL-induced illness or organ damage) *prior to initiating non-PBS-subsidised treatment with this drug for this condition*
AND
Clinical criteria:
Patient must have *had* a creatinine clearance greater than or equal to 70 mL/min *prior to initiating non-PBS-subsidised treatment with this drug for this condition*
AND
Clinical criteria:
Patient must have *had* a WHO performance status of 0 or 1 *prior to initiating non-PBS-subsidised treatment with this drug for this condition*
Prescriber Instruction:

There are more ibrutinib capsules in a pack than is required for the completion of a treatment cycle. The patient must not discard any remaining capsules after the completion of any treatment cycle as these capsules will be required for the doses in the final treatment cycle (i.e. treatment cycle 15).
Administrative advice: *Patients may qualify for PBS-subsidised treatment under this restriction once only. 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
Administrative advice: *This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria*

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IBRUTINIB					
ibrutinib 140 mg capsule, 90	NEW	1	90	4	Imbruvica

Restriction Summary / Treatment of Concept:
Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒ Authority Required (telephone/electronic via PBS Authorities system)~~ non-immediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart; requires at least one concept ID to be marked as 'FULL' for full assessment by Services Australia)~~
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 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
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 15x28 day cycles of PBS-subsidised treatment with this drug for this condition, whichever comes first.~~
Prescriber Instruction:

There are more ibrutinib capsules in a pack than is required for the completion of a treatment cycle. The patient must not discard any remaining capsules after the completion of any treatment cycle as these capsules will be required for the doses in the final treatment cycle (i.e. treatment cycle 15).

3.2 The requested effective ex-manufacturer price of ibrutinib is $[redacted], which was consistent with the existing effective price of ibrutinib in the relapsed/refractory (R/R) CLL/SLL setting. The pre-PBAC response applied a 5% reduction due to the 5-year statutory price reduction that it stated would be applied from 1 April 2023.

3.3 The sponsor of the submission is not the sponsor of venetoclax, however, the submission proposed the essential elements for venetoclax in combination with ibrutinib along with new initial and continuing restrictions.

3.4 The proposed restriction is consistent with, although narrower than, the proposed TGA indication for ibrutinib (previously untreated CLL/SLL).

3.5 The proposed restriction for initial treatment used an 'and' operator to combine clinical criteria defining fitness (cumulative illness rating scale (CIRS) score ≤6, creatinine clearance ≥70 mL/min, and WHO performance status 0-1), whereas the venetoclax + obinutuzumab restriction uses the 'OR' operator (CIRS score >6 OR creatinine clearance <70 mL/min). The evaluation considered that requiring three criteria to be satisfied may preclude use in some patients who would benefit from accessing treatment.

3.6 Patients with certain comorbidities were excluded from the CAPTIVATE study (most cancers, infection, cardiovascular disease, or stroke), however in practice the overlap with the CIRS, which considers a broader range of comorbidities, and the WHO performance status, which is based on ability to perform activities of daily living, may be incomplete. Patients with cardiovascular comorbidities may be eligible under the proposed restriction, despite the cardiovascular risk associated with treatment.

3.7 The requested restriction did not include a definition of progressive disease, however, this is consistent with the current venetoclax + obinutuzumab restriction for previously untreated CLL/SLL.

3.8 A grandfather restriction was also proposed. The submission anticipated that approximately < 500 patients will be grandfathered onto the PBS from a [redacted] (not yet commenced at the time of submission).

3.9 The proposed restriction will have flow-on changes to the current ibrutinib listing for R/R CLL/SLL (PBS item code 11213E). The submission requested that the listing of ibrutinib + venetoclax should not preclude patients being PBS eligible to receive subsequent BTK inhibitors, including ibrutinib, in the R/R setting. The submission did not propose any clinical criteria for ibrutinib re-treatment. This was inconsistent with the clinical trial, which limited re-treatment to relapsed patients who had previously completed the full course of ibrutinib + venetoclax combination therapy. Further, the Pre-Sub-Committee Response (PSCR) stated that the PBAC may wish to consider whether re-treatment with venetoclax should be permitted. Refer to paragraph 4.14 for further discussion regarding re-treatment.

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.

4.2 CLL is more common in men than women (65% versus 35%), with a mean age at diagnosis in Australia of 70 years (males 68.8 years, females 71.2 years). The five-year relative survival rate in Australia in 2011-2015 was 82.8% (AIHW, 2019). 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, whereas in SLL, abnormal lymphocytes are predominantly located in lymph nodes, bone marrow and other lymphoid tissue. The prognosis and aetiology of CLL and SLL are similar; therefore, the existing approaches to management, as well as treatment considerations are consistent with one another.

4.3 Characteristics associated with a worse prognosis include genetic factors (del17p/TP53 mutation, 11q deletion, unmutated IGHV), biochemical/cell surface markers (serum thymidine kinase, serum β2 microglobulin), and patient characteristics (male sex, older age, worse ECOG performance score). Del17p is found in 5-8% of chemotherapy-naïve patients, and is associated with resistance to genotoxic chemotherapies, including conventional chemoimmunotherapy regimens (Hallek, 2015).

4.4 CLL/SLL is generally a slowly progressing cancer with a relapsing, remitting course. Many patients are managed with a 'watch and wait' approach until symptoms develop. The choice of therapy depends on a number of factors, including age, fitness, comorbidities, and the presence of prognostic genetic mutations.

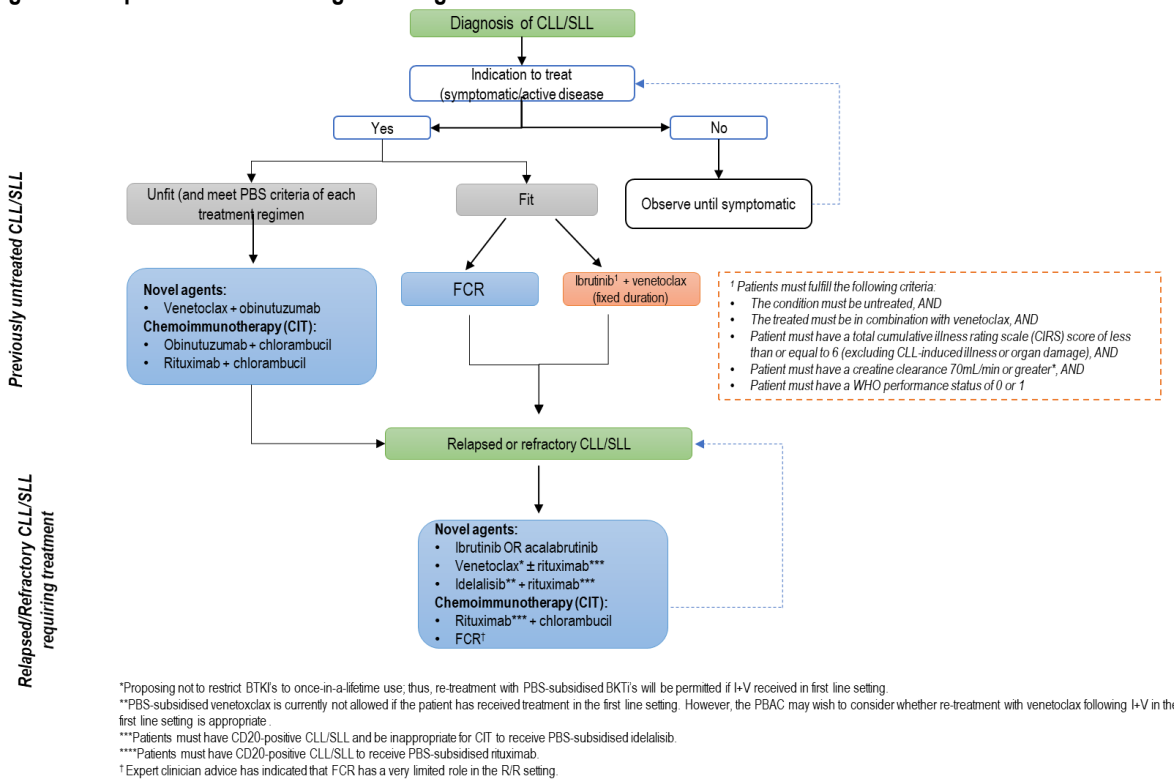
4.5 Ibrutinib is an orally administered small molecule inhibitor of BTK. In B cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. Through BTK inhibition, ibrutinib overcomes the B-cell antigen receptor and chemokine-controlled retention of malignant B-cells in their supportive microenvironments, thereby disrupting the pathogenesis of several B-cell malignancies such as CLL and SLL.

4.6 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.

4.7 The proposed clinical management algorithm is shown in Figure 1, and positions ibrutinib + venetoclax as a first-line option for fit patients who would otherwise be

treated with FCR. The submission noted that, based on expert clinical opinion, ECOG status, CIRS scores and age are key determinants of fitness of CLL patents, while creatinine clearance is a determinant of suitability for FCR. The alternative first-line treatment option included in the algorithm in this population (patients aged <65 years without significant comorbidities) was FCR. The ESC noted that FCR is not recommended for patients with del17p.

Figure 1: Proposed clinical management algorithm



*Proposing not to restrict BTKI's to once-in-a-lifetime use; thus, re-treatment with PBS-subsidised BKTi's will be permitted if I+V received in first line setting.
**PBS-subsidised venetoxclax is currently not allowed if the patient has received treatment in the first line setting. However, the PBAC may wish to consider whether re-treatment with venetoclax following I+V in the first line setting is appropriate.
***Patients must have CD20-positive CLL/SLL and be inappropriate for CIT to receive PBS-subsidised idelalisib.
****Patients must have CD20-positive CLL/SLL to receive PBS-subsidised rituximab.
† Expert clinician advice has indicated that FCR has a very limited role in the R/R setting.

Source: Figure 1-14, p48 of the submission
Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; FCR, fludarabine, cyclophosphamide, and rituximab

4.8 The treatment algorithm for CLL/SLL is rapidly evolving, with several new regimens being included in recent years on the basis of Phase III, head-to-head trials. The June 2022 National Comprehensive Cancer Network (NCCN) guidelines for the management of CLL/SLL list ibrutinib monotherapy, acalabrutinib +/- obinutuzumab, and venetoclax + obinutuzumab as the preferred first-line therapies for all patients (regardless of age, presence of comorbidities, or presence of del17p/TP53 mutation). The ESC noted that none of these agents or combinations are currently PBS listed for first-line use in the proposed population of fit patients (although ibrutinib as monotherapy was recommended by the PBAC for patients with del17p). The ESC further noted that the key PBS-listed treatment in fit patients, FCR, is only included in the NCCN guidelines as a later-line option and is poorly tolerated and associated with a risk of cytopenia and secondary malignancies. The ESC considered that Australia lags international guidelines in providing access to small molecule inhibitors (BTK inhibitors and/or B-cell lymphoma 2 (BCL2) inhibitors) in the first-line treatment of patients with

CLL and there is a high clinical need for alternate treatment options. The ESC noted that many patients in large centres across Australia access these treatments through compassionate access schemes (and that they may want to switch to ibrutinib + venetoclax).

4.9 Although fludarabine has an unrestricted PBS listing, it is only TGA indicated for the treatment of CLL. The use of fludarabine through the PBS has been declining with 5,361 prescriptions in 2018 compared with 2,533 prescriptions in 2021 and 1,620 prescriptions from January 2022 through to October 2022.[1] Based on the submission's assumption in the financial estimates that each patient receives on average 13.74 prescriptions (Table 13), it is likely that less than 150 patients ([1,620/10*12]/13.74) were treated with fludarabine in 2022.

4.10 Further, while the ESC considered that the requested restriction for ibrutinib + venetoclax was appropriate (i.e. first-line treatment in fit patients who would otherwise be suitable for FCR), it noted that in some cases there may also be a gap in the PBS availability of small molecule inhibitors for patients who are young (<65 years) and unfit (CIRS >6 and/or creatinine clearance <70 mL/min) despite this being a group with a high potential to benefit in the context of an indolent condition. This is because the existing restriction for venetoclax (a BCL2 inhibitor) in the first-line setting requires patients to be 'inappropriate for fludarabine based chemoimmunotherapy', which may in clinical practice include consideration of patient age (though age is not specifically referred to in the PBS restriction in the first-line setting). Further, these patients may not be able to access BTK inhibitors (acalabrutinib or ibrutinib) or venetoclax in the R/R setting (e.g., depending on response/progression-free interval following prior therapy, del17p status or presence of specific autoimmune conditions). The ESC considered that, while the listing requested in the resubmission was appropriate in the context of the clinical evidence provided, broader access to regimens containing small molecule inhibitors across both fit and unfit patients in the first-line setting may help address clinical need and equity of access.

4.11 The UpToDate guidelines note that although studies investigating a BTK inhibitor with venetoclax have been published, these combinations have not been directly compared with a continuous BTK inhibitor or fixed duration venetoclax plus obinutuzumab, and further study is needed prior to their routine clinical use.

4.12 The ESC considered that it was unclear whether the combination of ibrutinib + venetoclax offers a superior risk-benefit profile compared with single agent ibrutinib or venetoclax in the first-line setting, and that the contribution of each medicine to the combined treatment effect was unclear. The ESC considered that, in the absence

[1] Services Australia statistics, Pharmaceutical Benefits Scheme Item Reports, *Requested PBS and RPBS Items processed from January 2017 to October 2022 for Items 4393F, 7233Q and 9184J*. Accessed at Medicare Australia - Statistics - Pharmaceutical Benefits Schedule Item Statistics (humanservices.gov.au)

of such evidence, it may be preferable to use ibrutinib or venetoclax as a single agent first-line, or to use one of these therapies in combination with obinutuzumab/rituximab first-line. The ESC also considered that this may allow more flexibility regarding treatment options in the R/R setting, given the lack of evidence regarding re-treatment with the same agent. The pre-PBAC response stated that there are both clinical and patient-relevant benefits associated with ibrutinib + venetoclax having a fixed treatment duration of 15 cycles compared with single-agent ibrutinib in which patients are treated to progression.

4.13 In R/R disease, the proposed algorithm includes acalabrutinib monotherapy, ibrutinib monotherapy, venetoclax + rituximab, and idelalisib + rituximab as second/subsequent-line treatment options. In this setting, current PBS restrictions preclude patients from repeating treatment with BTK inhibitors (ibrutinib or acalabrutinib) or a venetoclax-based regimen. However, under the proposed treatment algorithm, the sponsor argued that PBS listing of ibrutinib + venetoclax in previously untreated CLL/SLL should not preclude the use of ibrutinib and other BTK inhibitors in the R/R setting. The evidence supporting re-treatment with BTK inhibitors in the R/R setting, following first-line ibrutinib + venetoclax, is limited. Re-treatment with venetoclax after first-line ibrutinib + venetoclax was not considered in the submission.

4.14 The ESC considered there was a lack of evidence regarding the effectiveness and safety of re-treatment with a BTK inhibitor or a BCL2 inhibitor as a second/subsequent line of therapy. The submission noted that nine relapsed patients (who completed the full treatment course of ibrutinib + venetoclax) received subsequent ibrutinib monotherapy but provided limited data on the outcomes of these patients. The PSCR indicated that all nine evaluable patients had achieved either a partial response (7 patients) or a complete response (2 patients) as their best response. However, the evaluation and the ESC considered there were insufficient clinical data to assess whether outcomes in the R/R setting were similar between ibrutinib-naïve and ibrutinib-experienced patients. Further, the submission provided no data on re-treatments with other BTK inhibitors or with venetoclax based regimens. Overall, the evaluation considered that the impact of first-line use of ibrutinib + venetoclax on downstream treatment options is unclear. The ESC noted that some studies have investigated single agent re-treatment after single-line therapy, but that none have investigated re-treatment with a single agent following first-line dual therapy. Further, the ESC considered that in practice, most clinicians would prefer to have the option to re-treat patients, given a clinically relevant treatment-free interval.

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

5 Comparator

5.1 The submission nominated FCR as the main comparator given that FCR is the treatment that will be replaced by ibrutinib + venetoclax, and that FCR is the only PBS-

listed treatment for the requested population. The PBAC noted that FCR is no longer recommended in international guidelines, or commonly used in clinical practice.

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 (16), health care professionals (1 group of clinicians) and from the 2 organisations, Lymphoma Australia, and the Leukaemia Foundation, via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with ibrutinib including improvements in disease progression, white blood cell counts, and energy levels. Individuals expressed a preference for targeted first-line therapy, like ibrutinib, given it enabled them to be treated at home, experience fewer side effects than chemotherapy, with several contributors expressed concerns about the toxicity of existing regimens, and retain a sense of normalcy throughout treatment including being able to remain employed and maintain social and emotional stability. While most comments described little to no side effects, one comment outlined the negative impact of ibrutinib treatment on their cardiovascular health. Many comments regarded the current cost of ibrutinib treatment as an obstacle to treatment, making chemotherapy their only current treatment option. Concerns about access to this class of drugs for younger and fitter patients were also raised in consumer comments.

6.3 The PBAC recalled that a clinician consultation was held on 1 December 2022 to discuss the treatment of CLL /SLL in relation to the existing PBS treatment algorithm and the new drug regimens proposed for PBS-listing in the context of the evolving treatment landscape. The key points were:

- The clinicians emphasised that FCR is no longer a preferred regimen in any patient group, which creates a significant access issue for young and/or fit patients who do not meet the existing PBS criteria for BTK inhibitors or venetoclax. The clinicians noted that, while the clinical need is highest in patients with poor risk cytogenetics, it would not be appropriate to limit access to BTKi and /or venetoclax therapy to these specific groups given the high clinical need across the broader young, fit population.
- The clinicians indicated that the existing PBS criteria around 'inappropriate for fludarabine-based chemoimmunotherapy' and 'unsuitable for treatment with a purine analogue' are no longer relevant to current clinical practice.
- The clinicians advised that there is a lack of clinical trial data available to differentiate between regimens or determine which particular regimen would

be preferable in a particular patient group/setting. Overall, the clinicians considered that it would be preferable to have a range of options available for all patients with CLL/SLL. The clinicians noted that any treatment option containing a BTKi and/or venetoclax would be preferable to FCR.

- The clinicians outlined that it would be appropriate to re-treat patients with venetoclax or BTKi therapy if they had progressed following these therapies (unless discontinued due to poor tolerability). The clinicians indicated that a longer duration of initial response was an indicator for a higher probability of responding to that same therapy again (and vice versa). The clinicians indicated that there were no firm data regarding a time-frame for a recurrence-free period after which it would be appropriate to re-treat with the same agent and advised that a range of variables would be taken into account such as patient age and treatment intent.

Clinical studies

6.4 In the absence of any head-to-head trials in the proposed population, the submission was based on an unanchored, unadjusted indirect treatment comparison of the single-arm ibrutinib + venetoclax fixed duration cohort of the CAPTIVATE study and the FCR arm of the ECOG1912 randomised trial.

6.5 The PBAC Guidelines note that indirect comparisons (such as a naïve comparison between single arms) are difficult to interpret and reduce the confidence of the PBAC in decision making. The ESC noted that where patient-level data are available for at least one study in the comparison, the Guidelines recommend using matching-adjusted indirect comparisons or simulated treatment comparisons to correct for trial differences to improve the transitivity of the comparison.

6.6 Details of the study reports presented in the submission are provided in Table 2.

Table 2: Studies and associated reports presented in the submission

Trial ID	Publication title	Publication citation
Ibrutinib + venetoclax studies		
CAPTIVATE	Phase 2 study of the combination of ibrutinib plus venetoclax in patients with treatment-naive chronic lymphocytic leukemia / small lymphocytic lymphoma. Tam, CS, Allan, JN, Siddiqi, T, et al. Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary analysis of the CAPTIVATE FD cohort.	Internal study report; 11 November 2021. Blood. 2022; 139(22): 3278-3289.
FCR trials		
ECOG1912	Shanafelt, TD, Wang, XV, Kay, NE, et al. Ibrutinib–rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. Shanafelt TD, Wang XV, Hanson CA, et al. Long-term Outcomes for Ibrutinib-Rituximab and Chemoimmunotherapy in CLL: Updated Results of the E1912 Trial.	New England Journal of Medicine. 2019; 381(5): 432-443. Blood. 2022;140(2): 112-120.

Source: Table 2-7, p76 of the submission.
Abbreviations: FCR, fludarabine, cyclophosphamide, rituximab

6.7 The submission identified a total of six trials of FCR for possible inclusion in the submission (ECOG1912, CLL-10, CLL-8, ADMIRE, FLAIR and ARCTIC). The submission claimed that results for progression-free survival and overall survival were similar across trials, however, significant variability in progression-free survival was apparent. The submission justified the use of ECOG1912 as the pivotal FCR trial used in the submission because data were relatively mature, the trial was recently conducted (i.e., post the availability of BTK inhibitors), and therefore represented the most recent clinical evidence of FCR in previously untreated fit CLL/SLL for which the sponsor had access to patient level data. The evaluation considered that it may have been more appropriate to use the pooled data and that it was unclear whether ECOG1912 is representative of FCR treatment in current clinical practice. The ESC considered that while the submission did not adequately justify the selection of ECOG1912, this was unlikely to substantially impact the conclusions given it was a relatively large trial.

6.8 The key features of the included studies are summarised in Table 3.

Table 3: Key features of the included evidence- naïve indirect comparison

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Ibrutinib + venetoclax						
CAPTIVATE FD cohort	159	Single-arm, open-label study Median duration of follow-up: - 12 November 2020; 27.9 months - 4 August 2021; 38.7 months	High	Age 18-70 years; adequate hematologic, hepatic, and renal function; diagnosis of CLL/SLL that meets IWCLL diagnostic criteria and requires treatment; ECOG score 0-2; no prior therapy for CLL	- Complete response rate - Progression-free survival - Overall survival - Overall response rate - MRD negativity rate - Adverse events	Progression-free survival, incidence of atrial fibrillation
FCR						
ECOG1912 FCR arm	175	Randomised trial of ibrutinib until disease progression + 6 cycles of rituximab versus 6 cycles of FCR Median duration of follow-up: - 17 July 2018; 33.6 months - 9 August 2021; 70 months	Low	Age ≤ 70 years; adequate hematologic, hepatic, and renal function; diagnosis of CLL/SLL that meets IWCLL diagnostic criteria and requires treatment; ECOG score 0-2; no prior therapy for CLL; without 17p deletion; able to tolerate FCR therapy	- Progression-free survival - Overall survival - Complete response rate - Overall response rate - MRD negativity rate - Health-related quality of life (FACT-Leu TOI) - Adverse events	Progression-free survival

Source: Section 3.2, p39; Section 3.6, p41; Section 3.9, p43 CAPTIVATE clinical study report; Shanafelt et al. (2019).
Abbreviations: CLL/SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; ECOG, Eastern Cooperative Oncology Group; FACT-Leu TOI, Functional assessment of cancer therapy- Leukaemia Trial Outcome Index; FCR, fludarabine, cyclophosphamide, rituximab; FD, fixed duration; IWCLL, International Workshop on Chronic Lymphocytic Leukemia; MRD, minimal residual disease

6.9 CAPTIVATE was a multicentre Phase 2 study assessing treatment with ibrutinib + venetoclax in previously untreated patients with CLL or SLL and included both a fixed duration (FD) treatment cohort (referred to in the clinical study report as the FD

cohort) and a minimal residual disease (MRD)-guided discontinuation cohort (referred to as the MRD cohort). The results of the FD cohort were presented in the submission, as the fixed duration treatment course aligns with the requested PBS listing (15 cycles; 3 cycle lead-in of ibrutinib monotherapy followed by 12 cycles of ibrutinib + venetoclax).

6.10 As a single arm phase 2 study, with a surrogate primary end-point of complete response rate as determined by the investigator, and no quality-of-life measures, the FD cohort of CAPTIVATE is considered to be at high risk of bias based on study design and use of a surrogate primary endpoint. The evaluation and the ESC considered that it was difficult to accurately quantify the magnitude of benefit with ibrutinib + venetoclax given the lack of comparative evidence and a reliance on surrogate endpoints without consideration of the impact on quality of life.

6.11 Patients with confirmed progression after completion of the fixed dose ibrutinib + venetoclax regimen could be re-treated with ibrutinib monotherapy; and patients who experienced durable efficacy (defined as time to progression after completion of fixed duration regimen of at least 2 years), were allowed to repeat treatment with ibrutinib + venetoclax, based on clinical discretion. A total of 9 patients were re-treated with ibrutinib monotherapy over the extended follow-up period for a median duration of 4.9 months.

6.12 ECOG1912 was a randomised, phase 3 trial of ibrutinib + rituximab versus FCR in previously untreated younger patients (≤70 years of age) with CLL. The primary objective of the trial was to evaluate the ability of ibrutinib + rituximab to prolong progression-free survival compared to FCR. Only the FCR arm was presented in the submission, given this was the nominated comparator.

6.13 There were some differences between the included studies in terms of eligibility criteria. Adequate liver and renal function were requirements for enrolment in both studies, however the cut offs differed. In CAPTIVATE, patients needed to have reported creatinine clearance (CrCl) of ≥60 mL/min, while ECOG1912 included patients with CrCl >40 mL/min. Patients with bilirubin levels of <1.5 times the upper limit of normal (ULN) were included in CAPTIVATE, while ECOG1912 included patients with bilirubin levels of ≤2.5 ULN. The thresholds for liver and renal function suggested that more unwell patients and/or patients at risk of adverse events may have been enrolled into ECOG1912 compared with CAPTIVATE, although the potential impact of this is unclear.

6.14 Baseline demographic characteristics were broadly similar between the separate study arms in terms of mean age and gender, and race. The populations differed in terms of a number of disease characteristics, including time since diagnosis (longer in CAPTIVATE), baseline ECOG score (higher proportion at 1-2 in ECOG1912), bulky disease (higher proportion >10 cm in ECOG1912), and cytopenia (a higher proportion with some abnormality in ECOG1912). Additionally, a higher proportion of patients in CAPTIVATE were classified as Rai stage 0/I/II (low risk) compared to patients enrolled

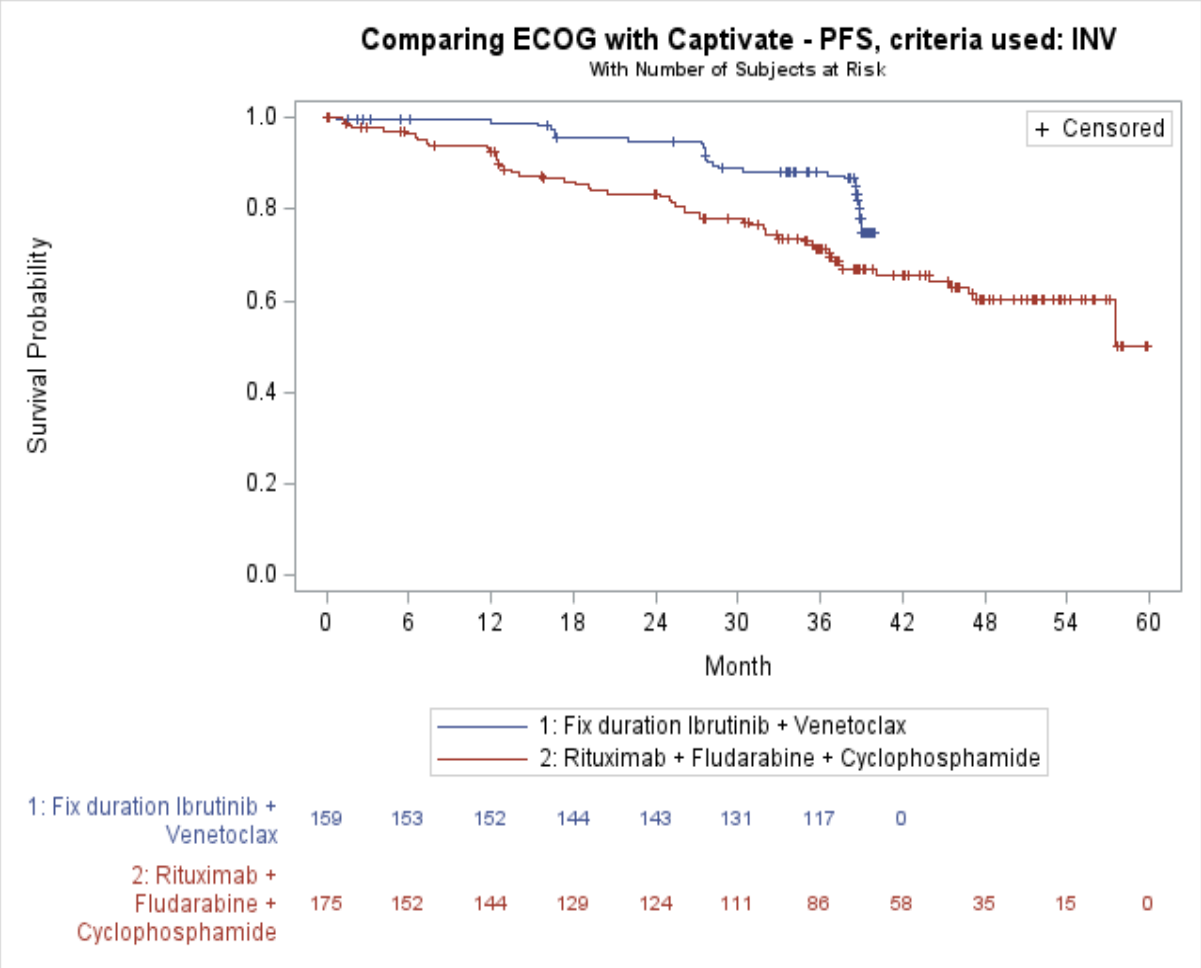
in ECOG1912 (71.1% in CAPTIVATE all-treated population vs 58.9% in ECOG1912). Rai staging is a clinical classification system for CLL that identifies different stages of disease prognosis; a lower Rai stage (0/I/II) indicates a better prognosis. Generally, markers of disease severity were worse in a higher proportion of patients in ECOG1912 compared with CAPTIVATE, which may potentially bias efficacy results in favour of ibrutinib + venetoclax versus FCR.

6.15 In CAPTIVATE, a protocol amendment (29 November 2018) suggested that the study was designed to investigate the treatment of patients without del17p, and these patients were excluded from enrolment thereafter. Twenty patients (12.6%) with del17p had been incidentally enrolled in the study prior to this amendment; due to the small size of this subgroup, results cannot be assumed to be generalisable to patients with del17p, who have worse prognosis than people without the deletion. In ECOG1912, patients with del17p were excluded from the trial because of the poor response of CLL in these patients to FCR. The ESC considered that exclusion of patients with this important prognostic factor in ECOG1912 may have favoured FCR.

Comparative effectiveness

6.16 Results for the naïve comparison of ibrutinib + venetoclax and FCR for progression-free survival, based on the FD cohort of the CAPTIVATE study, and the FCR arm of ECOG1912 are summarised in Figure 2 and Table 4 below.

Figure 2: Kaplan-Meier estimates of investigator assessed progression-free survival in FD cohort of CAPTIVATE (ibrutinib + venetoclax; 38.7 months median follow-up) and FCR arm of ECOG1912 (48 months median follow-up)



Source: Figure 2-14, p142 of the submission.
Abbreviations: INV, investigator-assessment; PFS, progression-free survival
* Note that the results presented in Figure 2 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for CAPTIVATE. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Table 4: Landmark estimates for progression-free survival based on investigator assessment in FD cohort of CAPTIVATE (ibrutinib + venetoclax; 38.7 months median follow-up) and FCR arm of ECOG1912 (48 months median follow-up)

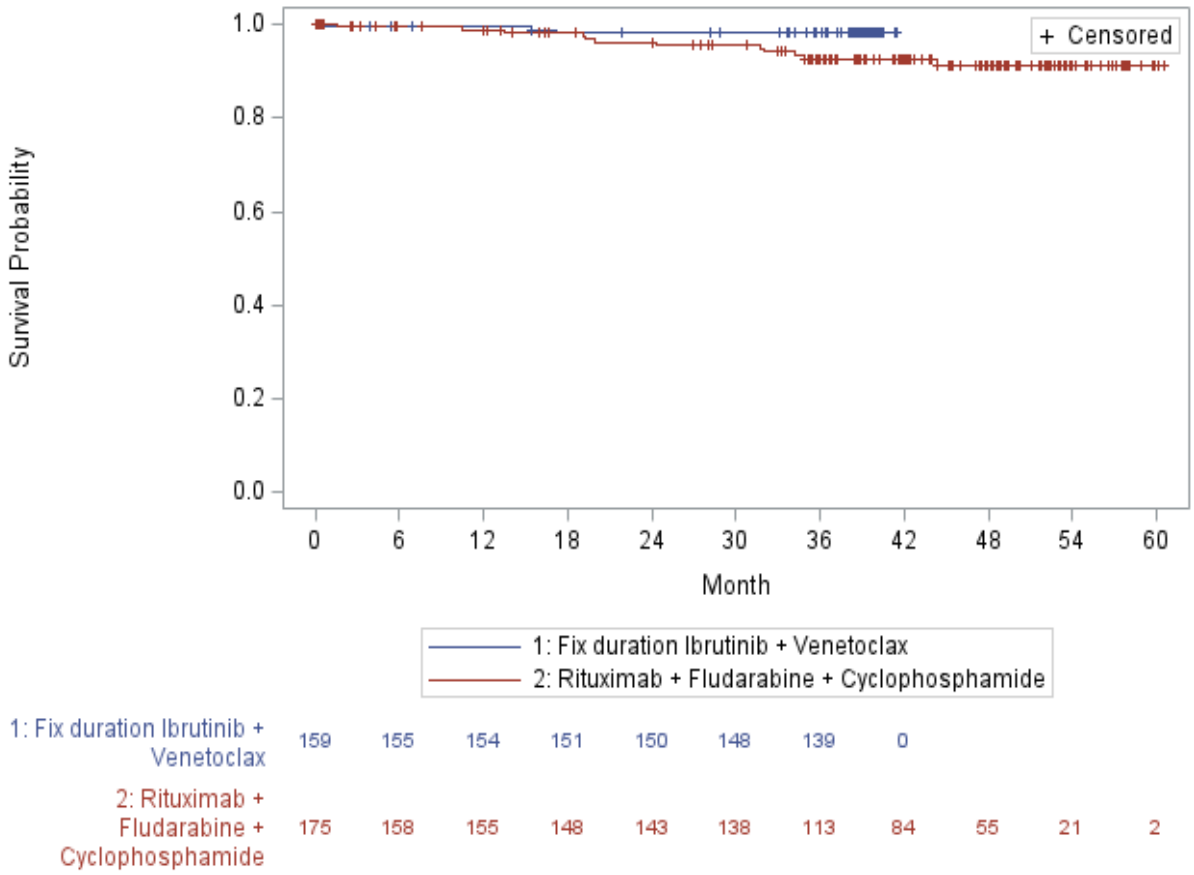
	CAPTIVATE (ibrutinib + venetoclax) N = 157	ECOG1912 (FCR) N = 175
Landmark estimates, % (95% CI)		
- 6 Months	99.37 (95.6, 99.9)	96.32 (92.0, 98.3)
- 12 Months	99.37 (95.6, 99.9)	92.51 (87.2, 95.7)
- 18 Months	95.43 (90.7, 97.8)	85.98 (79.5, 90.5)
- 24 Months	94.77 (89.8, 97.4)	83.31 (76.5, 88.3)
- 30 Months	88.74 (82.5, 92.9)	77.89 (70.4, 83.7)
- 36 Months	88.07 (81.7, 92.3)	71.27 (63.2, 77.7)

Source: Table 2-44, p142 of the submission.
Abbreviations: CI, confidence interval; FCR, fludarabine, cyclophosphamide, rituximab

6.17 The hazard ratio for progression-free survival derived in the naïve indirect comparison of ibrutinib + venetoclax (38.7 months median follow-up) versus FCR (48 months median follow-up) was 0.243 (95% CI: 0.151, 0.391; p <0.0001), in favour of ibrutinib + venetoclax. Similar results were derived using longer follow-up (median 70 months) for FCR (HR 0.204; 95% CI:0.13, 0.32; p <0.0001). The ESC noted that the progression-free survival rates reported in CAPTIVATE were consistently higher than in the FCR arm of ECOG1912 at all time points in the landmark estimates. The submission claimed that ibrutinib + venetoclax was statistically and clinically superior to FCR in prolonging progression-free survival. The estimated hazard ratio for PFS strongly favours ibrutinib + venetoclax, however should be interpreted with caution. There were some notable differences in the patient populations between the two included studies, including differences in comorbidities and severity of illness, and the resulting hazard ratio may not represent the true estimate of differences in treatment effect. The evaluation and the ESC considered that, in the absence of longer-term follow-up and comparative results, the magnitude of the benefit of combining ibrutinib and venetoclax compared with other first-line treatment options remains unclear.

6.18 Results for the naïve comparison of ibrutinib + venetoclax and FCR for overall survival, based on the FD cohort of the CAPTIVATE study, and the FCR arm of ECOG1912 are summarised in Figure 3 and Table 5 below.

Figure 3: Kaplan-Meier estimates of overall survival in the FD cohort of CAPTIVATE (ibrutinib + venetoclax, 38-month follow-up) compared with the FCR arm of ECOG1912 (48-month median follow-up)



Source: Figure 2-16, p145 of the submission.
* Note that the results presented in Figure 3 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for CAPTIVATE. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Table 5: Landmark estimates of overall survival for the FD cohort of CAPTIVATE (ibrutinib + venetoclax; 37.8 months median follow-up) and the FCR arm of ECOG1912 (48 months median follow-up)

	CAPTIVATE (ibrutinib + venetoclax) N = 157	ECOG1912 (FCR) N = 175
Landmark estimates, % (95% CI)		
• 6 months	99.37 (95.6, 99.9)	99.40 (95.8, 99.9)
• 12 months	99.37 (65.6, 99.9)	98.76 (95.2, 99.7)
• 18 months	98.08 (94.2, 99.4)	98.12 (94.3, 99.4)
• 24 months	98.08 (94.2, 99.4)	96.12 (91.6, 98.2)
• 30 months	98.08 (94.2, 99.4)	95.44 (90.7, 97.8)
• 36 months	98.08 (94.2, 99.4)	92.63 (87.1, 95.9)

Source: Table 2-46, p145 of the submission.
Abbreviations: CI, confidence interval; FCR, fludarabine, cyclophosphamide, rituximab

6.19 The hazard ratio derived in the naïve indirect comparison of ibrutinib + venetoclax (38.7 months median follow-up) versus FCR (48 months median follow-up) for the outcome of overall survival was 0.126 (95%CI: 0.035 to 0.453; p = 0.0015), in favour of

ibrutinib + venetoclax. Similar results were derived using longer follow-up (median 70 months) for FCR (HR 0.24; 95% CI:0.07, 0.82; p=0.023). The overall survival rates reported in CAPTIVATE for ibrutinib + venetoclax were the same or higher than those observed in the FCR arm of ECOG1912 at all time points from 6 months through to 36 months, by which time there was an approximate 5% difference in the absolute rates of overall survival. The submission claimed that ibrutinib + venetoclax was statistically superior to FCR in prolonging survival and reduced the risk of death by 87%. Survival data for both studies were immature and based on a relatively small number of events (i.e. 28 PFS events (investigator-assessed) and 3 OS events). The estimated hazard ratio is highly favourable towards ibrutinib + venetoclax, however should be interpreted with caution. There were notable differences in the patient populations between the two included studies, including differences in comorbidities and severity of illness, and the resulting hazard ratio may not represent the true estimate of differences in treatment effect. As treatment options for R/R disease improve, survival rates have improved. Increasingly, this means that overall survival in studies of first-line treatment options may be difficult to interpret. This was previously acknowledged by PBAC, that stated 'there may not be a difference [in overall survival] over the longer term given subsequent lines of effective therapy are available' (para 7.8, acalabrutinib Public Summary Document (PSD), November 2021 PBAC meeting). The ESC re-iterated the PBAC's previous advice that overall survival results in first-line CLL are difficult to interpret as they can be confounded by the subsequent lines of effective therapy available.

6.20 Patients who did progress in CAPTIVATE were offered subsequent therapy, however at the extended follow-up (3 years) rates were low; a total of 15 patients (9.4%) in the FD cohort of CAPTIVATE had received any subsequent therapy for CLL/SLL. A total of 9 patients were reintroduced to single-agent ibrutinib therapy following progressive disease (5.7%). Refer to paragraph 4.14.

6.21 The results of the naïve comparison of response per investigator assessment between the FD cohort of CAPTIVATE (ibrutinib + venetoclax; 38.7 months median follow-up) and the FCR arm of ECOG1912 (33.6 and 48 months median follow-up) are summarised in Table 6 below.

Table 6: Overall response rate in the FD cohort of CAPTIVATE versus the FCR arm of ECOG1912 per investigator assessment

	Ibrutinib + venetoclax (38.7 months follow-up) N=159	FCR (33.6 months follow-up) N=175	FCR (48 months follow-up) N=175
Complete response rate (CR, CRi); n (%)	91 (56.9)	53 (30.3)	NR
Overall response rate (CR, CRi, nPR or PR); n (%)	153 (96.2)	141 (80.6)	150 (85.7)

Source: Table 2-47, p147 of the submission.

Abbreviations: CR, complete response; CRi, complete response with incomplete bone marrow recovery; nPR, nodular partial response; NR, not reported/assessed; PR, partial response

6.22 A naïve indirect comparison between ibrutinib + venetoclax (median follow-up 38.7 months) versus FCR (median follow-up 33.6 months) for the absolute rates of complete response/complete response with incomplete bone marrow recovery suggested a statistically significant difference between treatments (odds ratio=3.08; 95% CI: 1.96, 4.83; p<0.001). Similar results were derived when comparing overall response rates (odds ratio=6.15; 95% CI: 2.51, 15.09; p<0.001).[2] The results of the naïve indirect comparison should be interpreted with caution given the differences in the patient populations between the two included studies. The resulting point estimates may not represent the true size of the treatment effect.

Comparative harms

6.23 For the unanchored, unadjusted indirect comparisons of safety, adverse event data were only available based on patient incidence, however event rates over time would be informative to consider (as individual patients may experience multiple events of the same type) given the differences in duration of treatment exposure between ibrutinib + venetoclax and FCR.

6.24 Table 7 below presents a summary of adverse events for both the FD cohort of CAPTIVATE and the FCR arm of ECOG1912.

Table 7: Comparison of adverse events reported in the FD cohort of CAPTIVATE (ibrutinib + venetoclax) and the FCR arm of ECOG1912

	CAPTIVATE FD cohort N=159 n (%)	ECOG1912 FCR arm N=158 n (%)
Any adverse event	158 (99.4)	157 (99.4)
Any grade ≥3 adverse event	99 (62.3)	142 (89.9)
Adverse events leading to discontinuation	8 (5.0)	NR
Any serious adverse event	36 (22.6)	NR
Adverse events leading to death	1 (0.6)	2 (1.3)
Adverse events of special interest		
• Atrial fibrillation	7 (4.4)	4 (2.5)
• Cardiac failure	1 (0.6)	0
• Tumour lysis syndrome	0	2 (1.3)

Source: Table 2-51, p149; Section 2.6.2.4, p151 of the submission.
Abbreviations: FCR, fludarabine, cyclophosphamide, rituximab

6.25 Overall, the proportion of patients reporting any adverse event was similar for patients who received ibrutinib + venetoclax or FCR. The proportion of adverse events of Grade 3 or above was higher in the FCR arm compared with the ibrutinib +

[2] Note that the results presented are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for CAPTIVATE. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

venetoclax arm. A low and similar proportion of patients between treatment arms experienced a fatal adverse event after receiving treatment.

6.26 The adverse event profile differed between treatments. The most commonly occurring adverse events associated with ibrutinib + venetoclax in the FD cohort of CAPTIVATE included diarrhoea (62.3%), nausea (42.8%), neutropenia (41.5%), arthralgia (33.3%), muscle spasms (29.6%), and headache (25.2%). The most commonly occurring Grade 3 or higher adverse events included neutropenia (32.7%), and hypertension (5.7%).

6.27 The most commonly reported adverse events associated with FCR in the ECOG1912 trial included anaemia (80.4%), nausea (63.9%), constipation (31.6%), vomiting (27.8%), headache (27.2%), diarrhoea (26.6%), macropapular rash (25.9%) and infusion related reactions (25.3%). The most commonly occurring Grade 3 or higher adverse events included anaemia (17.7%), febrile neutropenia (15.8%), hypertension (6.3%), hyperglycaemia (5.7%), and macropapular rash (5.1%).

6.28 In terms of adverse events of special interest, cardiac adverse events including atrial fibrillation and cardiac failure, and haemorrhagic events were reported more frequently with ibrutinib + venetoclax than with FCR. No cases of tumour lysis syndrome were reported in patients on ibrutinib + venetoclax, but cases were reported in 1.3% of the FCR-treated patients in ECOG1912. Cytopenia adverse events were differentially reported between treatment groups, with neutropenia and thrombocytopenia more commonly reported with ibrutinib + venetoclax, and febrile neutropenia more commonly reported with FCR. Secondary primary malignancies were more commonly reported in patients in the FCR arm of ECOG1912 (8.9%) than in patients receiving ibrutinib + venetoclax in the FD cohort of CAPTIVATE (5.0%). Given the differences in patient populations, differences between studies in terms of adverse events should be interpreted with caution.

6.29 Being based on a naïve indirect comparison, the ESC considered it difficult to make an assessment of the comparative harms.

Additional evidence considered during the evaluation

6.30 The MRD cohort of the CAPTIVATE study enrolled a similar population to the FD cohort, based on the same patient eligibility criteria as the FD cohort. In the MRD cohort, patients who completed 15 cycles of ibrutinib + venetoclax (with 3-cycle ibrutinib lead-in), continued one additional cycle of ibrutinib + venetoclax, during which MRD status was confirmed and tumour response was assessed. Patients with confirmed undetectable MRD (52.4% of the original cohort) were randomly assigned to double-blinded treatment with placebo or ibrutinib monotherapy until confirmed MRD relapse or disease progression. Over a median duration of follow-up of 31.3 months, one-year disease free survival (absence of MRD relapse, progression, or death) was not statistically significantly different between the placebo (95%) and ibrutinib arms (100%; difference: 4.7%; 95% CI: -1.5, 10.9; p = 0.15).

6.31 The CAPTIVATE clinical study report presented a comparison of progression-free survival in the FD and MRD cohorts of the CAPTIVATE study (including patients in the MRD cohort who did not have confirmed undetectable MRD and were randomly assigned to open-label ibrutinib monotherapy or continued ibrutinib + venetoclax). Compared with the FD cohort, the MRD cohort overall had a greater time to progression, possibly as most of this cohort received ongoing treatment with either ibrutinib monotherapy or ibrutinib + venetoclax following the initial 16 cycles of ibrutinib + venetoclax, excepting the group with confirmed undetectable MRD who were randomised to placebo.

6.32 Although the GLOW trial, which formed the basis of the TGA evaluation, was conducted in a population considered unfit for treatment with fludarabine-based chemoimmunotherapy, results were included in the commentary as supportive evidence from a randomised, double blinded clinical trial, assessing the treatment effect of ibrutinib + venetoclax in a previously untreated CLL/SLL population. GLOW compared 15 cycles of ibrutinib + venetoclax (with 3-cycle ibrutinib lead-in) with 6 cycles of chlorambucil + obinutuzumab. With a median follow-up of 27.7 months, progression-free survival was significantly longer for ibrutinib + venetoclax than for chlorambucil + obinutuzumab (HR 0.216; 95% CI:0.131, 0.357; p<0.001). More patients in the ibrutinib + venetoclax arm discontinued treatment (23%) compared to those in the chlorambucil + obinutuzumab arm (4.8%). The proportion of patients experiencing at least one Grade 3 or 4 adverse event was similar in each treatment arm (approximately 68%), however there were more serious adverse events reported in the ibrutinib + venetoclax arm (46% versus 28%). At the time of primary analysis there were 11 deaths in the ibrutinib + venetoclax arm and 12 in the chlorambucil + obinutuzumab arm, with no difference in overall survival (HR 1.048, 95%CI 0.454, 2.419).

Benefits/harms

6.33 The naïve indirect comparison presented in the submission did not allow for a quantitative comparison of the benefits and harms of ibrutinib + venetoclax and FCR. Accordingly, a benefits/harms table was not presented.

Clinical claim

6.34 The submission described ibrutinib + venetoclax as superior in terms of effectiveness, and at least non-inferior, with a different safety profile (including a reduced risk of developing secondary primary malignancies) in terms of safety compared to FCR.

6.35 The ESC considered the therapeutic conclusion was likely supported, noting the following:

- The clinical evidence was highly uncertain, being based on an unanchored, unadjusted (naïve) indirect comparison between two single study arms, with no statistical adjustments to account for differences in study population (e.g., Rai staging) or circumstances of use. Additionally, this approach inherently

underestimated the statistical uncertainty associated with other unknown confounders by effectively assuming that all data comes from the same source. As such, while the estimated hazard ratio for progression-free survival was highly favourable towards ibrutinib + venetoclax, it should be interpreted with caution.

- There were notable differences in the patient populations between the two included studies in terms of disease characteristics. While the evaluation noted that markers of disease severity were generally worse in a higher proportion of patients in ECOG1912 compared with CAPTIVATE, which may potentially favour of ibrutinib + venetoclax (paragraph 6.14), the ESC also noted that the CAPTIVATE trial included patients with del17p, while the ECOG1912 trial excluded del17p patients, which may have favoured FCR. Overall, the ESC considered that the patient populations were likely to be broadly similar.
- Overall survival in first-line treatment is difficult to interpret. As previously acknowledged by the PBAC, "there may not be a difference [in overall survival] over the longer term given subsequent lines of effective therapy are available" (para 7.8, acalabrutinib PSD, November 2021 PBAC meeting).
- There were insufficient long-term data available to assess whether clinical outcomes for ibrutinib + venetoclax versus FCR may converge over time after the fixed duration treatment periods.

6.36 The ESC noted that in practice, the requested listing would move small molecule inhibitors (BTKi and/or BCL2 inhibitor-based regimens, which are currently available in the R/R setting) to an earlier line in the treatment algorithm. The ESC considered that the magnitude of benefit, particularly in terms of overall survival, of the existing treatment algorithm versus the proposed algorithm was unclear.

6.37 The PBAC considered that while the claim of superior comparative effectiveness versus FCR was likely met, the extent of the benefit was highly uncertain given the naïve nature of the comparison (i.e. based on an unanchored, unadjusted indirect comparison) and the immaturity of the data.

6.38 The PBAC considered that, while the naïve indirect comparison presented did not allow for a quantitative comparison of the harms of ibrutinib + venetoclax versus FCR, a claim of non-inferior comparative safety may be reasonable.

Economic analysis

6.39 The submission presented a modelled economic evaluation of ibrutinib + venetoclax compared with FCR for previously untreated patients with CLL/SLL, who would be considered fit for fludarabine based chemoimmunotherapy. The economic evaluation was based on a naïve indirect comparison of the single-arm FD cohort of the CAPTIVATE study (ibrutinib + venetoclax) and the FCR arm of the ECOG1912 randomised trial, and additional modelled data. The type of economic evaluation presented was a cost-effectiveness/cost-utility analysis.

Table 8: Key components of the economic evaluation

Component	Description
Treatments	Ibrutinib + venetoclax in the first-line setting followed by ibrutinib monotherapy on disease progression. Fludarabine, cyclophosphamide and rituximab (FCR) in the first-line setting followed by ibrutinib monotherapy on disease progression.
Time horizon	20 years in the model base case versus median follow-up of 39 months in the fixed duration cohort of the CAPTIVATE study and 65 months in the ECOG1912 trial.
Outcomes	Life years; quality adjusted life years
Type of analysis	Cost-effectiveness analysis and cost-utility analysis
Methods used to generate results	Markov state transition model
Health states	Two health states: free of progression; and combined progressed/dead state
Cycle length	One month
Transition probabilities	Monthly probabilities of progression were derived from Kaplan Meier progression-free survival curves, extrapolated to 20 years using a single generalised gamma function with treatment group included as a covariate. Patients with disease progression move to the combined progressed/dead health state, where it is assumed that all patients remain for the same fixed duration based on survival of 5.45 years, based on the ibrutinib arm of the economic model in the ibrutinib R/R CLL/SLL submission recommended by the PBAC in January 2017(Ibrutinib November 2016 PSD with addendum, November 2016 PBAC meeting). Monthly probabilities of death from the free of progression health state were based on ABS life tables (2018-2020) using age and sex characteristics at baseline from the fixed duration cohort of the CAPTIVATE study.
Costs	Drug costs associated with first-line ibrutinib + venetoclax and FCR were based on PBS prices and use of therapies derived from individual patient data in the CAPTIVATE and ECOG1912 studies*. Administration costs for FCR were based on the cost of AR-DRG R63Z (chemotherapy) with pharmacy costs removed. Disease management costs were based on MBS fees for GP and specialist visits and assumed frequencies of visits. Costs associated with tumour lysis syndrome management were not included.* Monitoring costs were based on the MBS fee for an ECG, assumed to occur at baseline for ibrutinib + venetoclax patients. Adverse event costs were applied to the ibrutinib + venetoclax arm only, based on the incidence of atrial fibrillation in the CAPTIVATE study, and the DPMQ of apixaban. Discounted total costs associated with ibrutinib in the R/R CLL/SLL model (Ibrutinib November 2016 PSD with addendum, November 2016 PBAC meeting) were applied to patients on disease progression, including the costs of ibrutinib (based on use in the RESONATE trial) and adverse event costs (based on the incidence of events in RESONATE and relevant AR-DRGs).
Health outcomes	Progression-free utility (0.82) was based on the utility of patients free of progression (off treatment) in a published economic evaluation (Howard 2017). On disease progression, patients are assigned the total discounted QALYs from the ibrutinib arm of the economic model used for ibrutinib in R/R CLL/SLL (Ibrutinib November 2016 PSD with addendum, November 2016 PBAC meeting). As such, the discounted QALYs (3.559) were applied on progression, informed by utilities derived from individual patient data from the RESONATE trial: baseline utility (0.763), progression-free (0.798) and progressive disease (0.735). It was assumed that there is no utility loss due to treatment toxicity/adverse events.
Software package	TreeAge Pro (Healthcare) version 2022.1.2 and Microsoft Office 365 Excel

Source: Table 3-1, p167 of the submission.

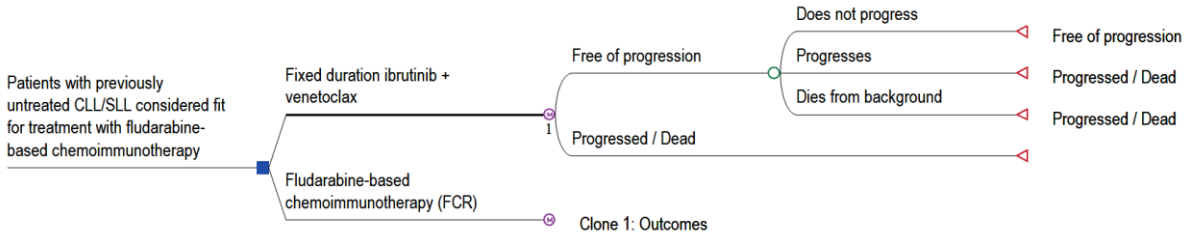
*Note: Revisions to these parameters were made in the revised economic model submitted with the pre-PBAC response.

Abbreviations: ABS, Australian Bureau of Statistics; CLL, chronic lymphocytic leukaemia; SLL, small lymphocytic lymphoma.

6.40 The submission nominated a 20-year time horizon for the economic model on the basis that this was appropriate to capture the majority of costs and benefits in a population with previously untreated CLL and an average age of 58 years at model entry. The submission argued that the patient population is younger and fitter than in previously untreated CLL/SLL populations for which the PBAC has preferred shorter time horizons of 10 years, which were based on either unfit, older, more frail patients (venetoclax PSD, March 2020 PBAC meeting, acalabrutinib PSD, July 2020 PBAC meeting), or those with adverse features such as del17p mutation (ibrutinib PSD, November 2019 PBAC meeting). While the ESC considered the 20-year horizon may be appropriate given the patient population comprises younger and fitter patients, it also considered the longer time horizon was associated with additional uncertainty given the extrapolation of outcomes based on a median follow-up of 39 months for ibrutinib + venetoclax.

6.41 Figure 4 illustrates the structure of the economic model.

Figure 4: Structure of the Markov model



Source: Figure 3-2, p 172 of the submission.
Abbreviations: CLL/SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; FCR, fludarabine, cyclophosphamide, and rituximab

6.42 Patients enter the model upon initiation of first-line treatment in the progression-free health state. Patients can either remain in the progression-free health state, or transition to the progressed/dead health state. Patients can transition into the progressed/dead health state via either:

- Experiencing progression of disease, where they are assigned costs and outcomes based on the results of the R/R ibrutinib model in the submission recommended by the PBAC (Ibrutinib November 2016 PSD with addendum, November 2016 PBAC meeting).
- Dying due to general population mortality.

6.43 The progressed/dead health state is the absorbing state in the Markov model, with no further transitions included in the economic model.

6.44 The evaluation and the ESC considered that the submission did not adequately justify the use of a 2-health state model but noted that overall survival in the FD cohort of the CAPTIVATE study was immature, which precluded the development of an acceptable partitioned survival analysis model. The ibrutinib R/R CLL/SLL model, which informs the progressed/dead health state, was a 3-state model (progression-free, progressive disease, dead) over a 10-year time horizon, based on evidence from the

RESONATE trial, which compared ibrutinib with ofatumumab in R/R CLL/SLL. The applicability of this evidence to the population included in the first-line model once they progress was not addressed in the submission, and it is not clear whether these populations align.

6.45 The submission claimed that by assigning the previously accepted outcomes for patients with R/R CLL/SLL, the model structure was able to adequately capture the disease pathway and introduce as few additional assumptions as possible beyond what has previously been accepted. The PSCR and pre-PBAC response further argued that the costs and benefits associated with ibrutinib in the R/R setting can be considered representative of costs and outcomes for other BTKis or venetoclax in the R/R setting given that the therapies have been listed on a cost-minimisation basis relative to each other; and the submission assumed ibrutinib + venetoclax in the first-line setting does not impact on the efficacy of downstream interventions.

6.46 The ESC considered the two-state model structure was overly simplistic and unlikely to reflect the costs and consequences of previously untreated CLL/SLL patients who are likely to experience multiple lines of subsequent therapy and periods of disease remission and relapse over their lifetime. The PBAC considered it was unclear whether the health outcomes associated with ibrutinib in the BTK inhibitor-naïve R/R setting of the ibrutinib R/R submission will be the same as the proposed population once they have progressed.

6.47 The pre-PBAC response provided two example models to demonstrate that the two-state model approach proposed, with costs and QALYs being applied from a separate R/R model, generates consistent results (in terms of costs and QALYs) to a more complex Markov model that includes the transitions from the R/R model. The pre-PBAC response stated that this "demonstrates the validity of the submitted two-state model compared to alternative more complex approaches". As the example models were not evaluated it was not possible to determine the accuracy of these statements.

6.48 Key drivers of the economic model are summarised in Table 9 below.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Probability of disease progression	The probabilities of disease progression were based on Kaplan Meier progression-free survival data from two separate sources, the FD cohort of the CAPTIVATE study (ibrutinib + venetoclax) and the FCR arm of the ECOG1912 trial, which were combined into a single analysis without any further statistical adjustment (a naïve comparison), assuming that the only difference between treatment groups was due to the treatment effects rather than any other differences between studies. A single parametric model (generalised gamma) was used to extrapolate PFS data beyond the duration of the studies, with treatment group included as a covariate, assuming proportional hazards. This was not adequately justified in the submission, an assessment of the proportional hazards assumption was not conducted, and the evaluation and the ESC considered none of the parametric models were a good visual fit for the ibrutinib + venetoclax Kaplan Meier data. The ESC noted that the PSCR provided an assessment of proportional hazards that suggested the proportional hazards assumption was not violated. The submission did not explore the use of more flexible approaches, however flexible parametric curves were assessed in the PSCR with the PSCR stating that this approach did not result in a better fit than the standard parametric models. Overall, the ESC considered that the submission's extrapolation of the naïve comparison of PFS curves resulted in large differences between treatment arms over the 20-year time horizon, which may not be realised in clinical practice.	High, favours ibrutinib + venetoclax.
Outcomes in progressed disease	Due to the model structure, patients accrue the total costs and consequences associated with disease progression (based on the results of the ibrutinib R/R CLL/SLL model), as an event (accrued up front at the time of progression), rather than accruing over time like a health state. Given that the estimated survival in the ibrutinib arm of the R/R model was 5.5 years, any progression that occurs after 14.5 years will accrue costs and benefits beyond the 20-year time horizon. A higher proportion of patients in the ibrutinib + venetoclax arm move from progression-free to the progressed/dead health state during the final 5.4 years of the model (10.6% versus 3.4% in the FCR arm), and therefore accrue the additional benefits beyond the time horizon intended in the present first-line model, favouring the ibrutinib + venetoclax treatment arm. It was unclear whether the health outcomes associated with ibrutinib in the BTK inhibitor-naïve R/R setting of the ibrutinib R/R submission will be the same as the proposed population once they have progressed.	High, favours ibrutinib + venetoclax.
Costs of tumour lysis syndrome management	In the FD cohort of the CAPTIVATE study, hospitalisation based on tumour lysis syndrome (TLS) risk and creatinine clearance, was observed for 39.6% of patients at baseline and 17.6% of patients after 3 cycles of ibrutinib monotherapy lead-in. Rasburicase, a treatment often used for TLS prophylaxis, was used in 5.0% of patients. The costs associated with TLS risk reduction were not included in first-line disease management costs in the economic evaluation. The evaluation and the ESC considered that exclusion of these costs from the economic evaluation was inappropriate and would underestimate the costs associated with ibrutinib + venetoclax (refer to paragraph 6.50). The pre-PBAC response provided a revised economic model that incorporated the costs of resources used in the prevention or treatment of TLS and hospitalisation costs.	Moderate, favours ibrutinib + venetoclax

Source: Constructed during the evaluation.
Abbreviations: CLL/SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; FCR, fludarabine, cyclophosphamide, and rituximab FD, fixed duration; PBAC, Pharmaceutical Benefits Advisory Committee; TLS, tumour lysis syndrome

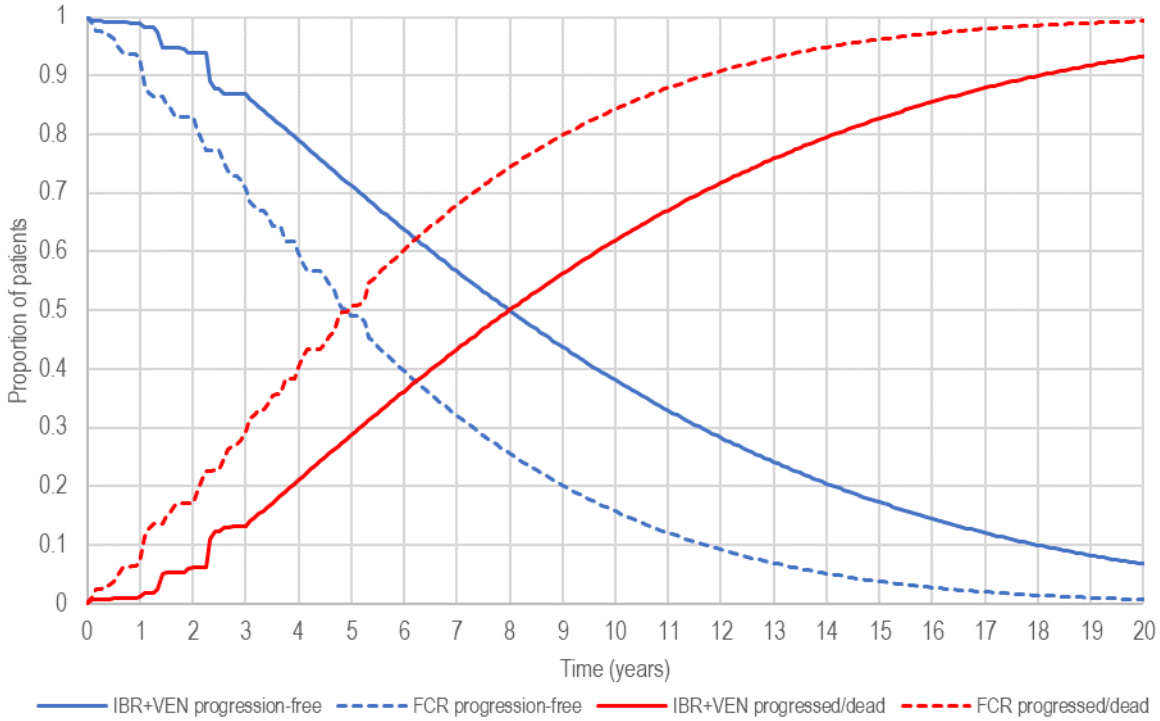
6.49 The utility associated with the progression-free health state was based on a published cost-effectiveness analysis (Howard 2017). The utility is consistent with the estimate for progression-free survival without therapy (0.82) from Kosmas 2015, which has been used as the source of utilities in other submissions to the PBAC for previously

untreated CLL/SLL. However, Kosmas 2015 also assessed the utility associated with progression-free survival in patients on initial oral therapy (0.71) and patients on initial IV therapy (0.67). The submission did not incorporate disutilities associated with treatment toxicity or adverse events, which may favour ibrutinib + venetoclax given the longer duration of treatment compared to FCR.

6.50 In the FD cohort of the CAPTIVATE study, hospitalisation based on tumour lysis syndrome (TLS) risk and creatinine clearance, was observed for 39.6% of patients at baseline and 17.6% of patients after 3 cycles of ibrutinib monotherapy lead-in. The costs associated with TLS risk reduction were not included in first-line disease management costs in the economic evaluation. The evaluation considered that the exclusion of these costs was inappropriate and would underestimate the costs associated with ibrutinib + venetoclax. The PSCR argued against including costs associated with TLS stating that these were protocol-driven within the CAPTIVATE study (due to a cautious 3-month lead-in period with ibrutinib, which the PSCR stated leads to tumour debulking decreasing the TLS risk category). The PSCR further stated that no patients in the fixed dose cohort of CAPTIVATE developed TLS, which the ESC considered was likely due to the conservative protocol-driven risk reduction of TLS within the study, and that this may have resulted in the trial overestimating hospitalisations. The ESC considered that in clinical practice hospitalisations for TLS would still be expected to occur, although this would likely be at a lower rate than observed within the trial setting. The ESC considered the cost of TLS management/prevention should therefore be included within the model, and that it may be appropriate to apply 50% of the hospitalisation rate observed in the trial. The pre-PBAC response provided a revised economic model that incorporated the cost of resources used in the prevention or treatment of TLS as well as hospitalisation costs which it stated were consistent with the approach described by the ESC.

6.51 Figure 5 below presents the model traces for the ibrutinib + venetoclax and FCR arms.

Figure 5: Model traces for the ibrutinib + venetoclax and FCR arms



Source: Figure 3-7, p190 of the submission.
Abbreviations: FCR, fludarabine, cyclophosphamide and rituximab; IBR, ibrutinib; VEN, venetoclax

6.52 The model traces indicate that treatment with ibrutinib + venetoclax was associated with a large increase in progression-free survival (and a corresponding reduction in progressed disease/death) compared to FCR. The curves diverge until approximately 7 years (at which point 55.5% of patients in the ibrutinib arm are progression-free, compared with 30.9% of patients in the FCR arm), when the curves begin to converge over time. The model traces indicated that 6.7% of patients in the ibrutinib + venetoclax arm and 0.7% of patients in the FCR arm remained progression-free at 20 years. The ESC considered it was plausible that some patients may be progression-free at 20 years, but that the large differences in progression-free survival between treatment arms over the 20-year time horizon was not adequately justified by the existing clinical data.

6.53 In the model, 7.0% of patients in the ibrutinib + venetoclax arm and 3.7% in the FCR arm die from the progression-free health state due to general population mortality, as a result of the longer time spent in the progression-free health state for the ibrutinib + venetoclax arm.

6.54 The results of the stepped economic evaluation provided in the submission are summarised in Table 10 below.

Table 10: Results of the stepped economic evaluation provided in the submission

Step and component	Ibrutinib + venetoclax	FCR	Increment
Step 1: Modelled analysis based on 39-month time horizon (median follow-up in the FD cohort of CAPTIVATE); life years generated in the progression-free health state; drug costs, treatment administration costs and costs of treating adverse events; no discounting			
Costs	$	$	$
Life years	3.0576	2.7436	0.3140
Incremental cost per life year gained			$[1]
Step 2: Time horizon extended to 20 years; first-line monitoring costs and second-line treatment costs added; second-line outcomes added; discounting applied			
Costs	$	$	$
Life years	9.6332	8.2135	1.4197
Incremental cost per life year gained			$[2]
Step 3: Utility weights applied			
Costs	$	$	$
QALYs	7.7262	6.5201	1.2061
Incremental cost per QALY gained			$[3]

Source: Table 3-7, p188 of the submission.
Abbreviations: FCR, fludarabine, cyclophosphamide and rituximab; FD, fixed duration; QALY, quality adjusted life year

The redacted values correspond to the following ranges:
[1]$155,000 to < $255,000
[2]$25,000 to < $35,000
[3]$35,000 to < $45,000

6.55 The extrapolation of costs and outcomes to 20 years had the largest impact on the results of the stepped economic evaluation.

6.56 Based on the modelled economic evaluation, treatment with ibrutinib + venetoclax was associated with an incremental cost per QALY gained of $35,000 to < $45,000 compared to fludarabine-based chemoimmunotherapy (FCR) for the treatment of previously untreated CLL/SLL. The effective price of venetoclax was estimated based on the effective price per pack of venetoclax in the R/R setting (which the submission stated was known to the sponsor).

6.57 The pre-PBAC response provided an updated model that included: (a) the costs of resources used in the prevention or treatment of TLS including hospitalisation costs; (b) a 5% reduction to the ibrutinib price due to the 5-year statutory price reduction that is expected to be applied from 1 April 2023; and (c) dose intensity adjustments for ibrutinib (95.4%) and venetoclax (93.1%), consistent with the financial estimates. The pre-PBAC response stated that the revised base case ICER is $35,000 to < $45,000/QALY.

6.58 On average, for every patient treated with ibrutinib + venetoclax versus FCR and followed up for 20 years, the submission's economic evaluation (undiscounted) estimated that there would be:

- Additional first-line drug costs of $, with additional monitoring ($759) and adverse event ($445) costs.
- Reduced costs associated with FCR drug administration ($14,259) and second-line treatment (ibrutinib monotherapy and related adverse event hospitalisations; $5,832).

- An additional 1.4 years of life, with the majority of time spent free of disease progression, associated with higher quality of life.

6.59 Table 11 summarises the results of key sensitivity analyses presented in the submission and conducted during the evaluation.

Table 11: Results of key sensitivity analyses (based on submission's model)

Analyses	Incremental cost	Incremental QALYs	ICER	% change from base case
Base case	$[redacted]	**1.2061**	$[redacted][1]	**-**
Discount rate (base case 5% costs and outcomes)				
- 0% costs and outcomes	$[redacted]	2.3121	$[redacted][2]	-44%
- 3.5% costs and outcomes	$[redacted]	1.4643	$[redacted][3]	-16%
Time horizon (base case 20 years)				
- 5 years	$[redacted]	-0.2653	Dominated	-
- 10 years	$[redacted]	0.3766	$[redacted][4]	+189%
- 15 years	$[redacted]	0.9366	$[redacted][5]	+24%
Progression-free survival (base case single parametric function fitted with treatment term; generalised gamma)				
- Weibull	$[redacted]	1.2103	$[redacted][1]	-1%
- Gompertz	$[redacted]	0.9267	$[redacted][6]	+40%
- generalised gamma; adjust treatment covariate (×75%)	$[redacted]	1.0399	$[redacted][5]	+20%
- generalised gamma; adjust treatment covariate (×50%) **[A]**	$[redacted]	0.8685	$[redacted][6]	+48%
- generalised gamma; adjust treatment covariate (×25%)	$[redacted]	0.6952	$[redacted][7]	+90%
Progression-free health state utility (base case 0.82 based on Howard 2017)				
On/off-treatment utility based on Kosmas 2015[a]	$[redacted]	1.1495	$[redacted][1]	+5%
QALYs in progressive disease (base case 3.559)				
- increase by 50% **[B]**	$[redacted]	0.9493	$[redacted][5]	+27%
- decrease by 50% **[C]**	$[redacted]	1.4629	$[redacted][3]	-18%
Costs in progressive disease (base case $62,760)				
- increase by 50%	$[redacted]	1.2061	$[redacted][1]	-9%
- decrease by 50%	$[redacted]	1.2061	$[redacted][1]	+9%
Multivariate analyses				
- **A:** Progression-free survival - generalised gamma; adjust treatment covariate (×50%) - **B:** QALYs in progressive disease: increase by 50%	$[redacted]	0.7062	$[redacted][6]	82%
- **A**: Progression-free survival - generalised gamma; adjust treatment covariate (×50%) - **C:** QALYs in progressive disease: decrease by 50%	$[redacted]	1.0307	$[redacted][5]	25%
- 15-year time horizon - **A** Progression-free survival - generalised gamma; adjust treatment covariate (×50%) - **B:** QALYs in progressive disease: increase by 50%	$[redacted]	0.5482	$[redacted][7]	+130%
- 15-year time horizon - **A**: Progression-free survival - generalised gamma; adjust treatment covariate (×50%) - **C** QALYs in progressive disease - decrease by 50%	$[redacted]	0.9307	$[redacted][5]	+35%

Source: Table 3-9, p191 of the submission; 'I plus V - 1L CLL-SLL model' TreeAge model provided with the submission.
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years
[a] 0.71 in the ibrutinib + venetoclax arm for 15 cycles; 0.67 in the FCR arm for 6 cycles; 0.82 in subsequent cycles

The redacted values correspond to the following ranges:
[1]$35,000 to < $45,000

[2]$15,000 to < $25,000
[3]$25,000 to < $35,000
[4]$95,000 to < $115,000
[5]$45,000 to < $55,000
[6]$55,000 to < $75,000
[7]$75,000 to < $95,000

6.60 The model was most sensitive to the time horizon, the discount rate, the treatment effect for progression-free survival, and QALYs applied to patients on disease progression. The model generates higher QALYs in the FCR arm than in the ibrutinib + venetoclax arm over short time horizons (≤7 years) due to the higher probability of progression and subsequent transition to the progressed/dead health state in the FCR arm, which results in the attribution of multiple QALYs upfront at the time of progression, which would otherwise be accrued beyond the time horizon.

6.61 The ESC considered that multivariate analyses varying both the treatment covariate and the number of QALYs due to disease progression were informative in demonstrating the sensitivity of the model to these parameters. In particular, the ESC noted that a multivariate sensitivity analysis which made the following changes:

- adjusted the treatment covariate for progression-free survival by 50%; and
- increased the QALYs in progressive disease by 50%
- increased the ICER to $55,000 to < $75,000 per QALY.

6.62 The impact of key issues with the model (such as the underlying clinical data and model structure) was unable to be tested in sensitivity analyses. The ESC considered this made it difficult to assess the sensitivity of the model to these key areas of uncertainty.

6.63 The economic model included offsets for reduced use of ibrutinib in subsequent lines. Removal of these offsets increased the ICER/QALY from $35,000 to < $45,000 to $45,000 to < $55,000, which indicates the importance of these costs in the submission's assessment of cost-effectiveness. While the PSCR stated that removal of the costs associated with subsequent lines but not the benefits would bias in favour of FCR, the ESC noted that these costs were, inappropriately, not included in the financial estimates or an RSA proposal.

Drug cost/patient/course

6.64 There were differences between the economic model and financial estimates in the number of scripts per patient per course. In the economic model, script numbers were based on the duration of treatment derived from individual patient data from CAPTIVATE and ECOG1912, whereas, in the financial estimates, script numbers were derived from time to treatment discontinuation Kaplan Meier curves and dose intensity estimates from individual patient data from CAPTIVATE for ibrutinib and venetoclax, and from estimates of persistence and dose intensity from individual patient data from ECOG1912 for FCR. There were also differences in the unit costs of fludarabine, cyclophosphamide and rituximab, based on average dispensed price in the economic model and DPMA in the financial estimates. No justification was

provided for the different approaches used. The ESC considered there should be greater consistency between the economic model and financials estimates in estimating script numbers and unit costs. The revised economic model submitted with the pre-PBAC response incorporated: (a) adjustments to the dose intensity for ibrutinib and venetoclax, aligning the dose intensity used in the economic model with that used in the financial estimates; and (b) a 5% reduction in the ibrutinib price due to the 5-year statutory price reduction that is expected to be applied from 1 April 2023. Neither of these changes are incorporated in the table below.

Table 12: Drug cost per patient for proposed and comparator drugs (based on submission)

	Clinical study	Economic model	Financial estimates
Ibrutinib + venetoclax (CAPTIVATE FD cohort)			
IBRUTINIB			
- proposed effective DPMQ	-	$	$
- compliance	Average duration of treatment 13.3 months; relative dose intensity 95.4%	13.38 scripts[a]	12.76 scripts (13.38 scripts × 95.4% dose intensity)[b]
- cost per course	-	$	$
VENETOCLAX			
- assumed effective DPMQ[c]	-	$ (initial)/ $ (continuing)	$ (initial)/ $ (continuing)
- compliance	Average duration of treatment 11.1 months; relative dose intensity 93.1%	0.96 initial scripts; 10.47 continuing scripts[a]	1 initial script × assumed 100% dose intensity; 9.70 continuing scripts (10.42 scripts × 93.1% dose intensity)[b]
- cost per course	-	$	$
Total cost per course	-	**$**	**$**
FCR (ECOG1912)			
FLUDARABINE			
- cost per pack	-	Average dispensed price per administration: $150.08[d]	Weighted DPMA: $177.33[e]
- compliance	Average no. cycles: 5 67.1% pts received 6 cycles	15.06 scripts[a]	13.74 scripts (18 scripts × 83.6% persistence × 91.3% dose intensity)[f]
- cost per course	-	$2,260	$2,436
CYCLOPHOSPHAMIDE			
- cost per pack	-	Average dispensed price per administration: $130.07[d]	Weighted DPMA: $185.40[e]
- compliance	Average no. cycles: 5 67.1% pts received 6 cycles	15.06 scripts[a]	13.94 scripts (18 scripts × 83.6% persistence × 92.6% dose intensity)[f]
- cost per course	-	$1,959	$2,584
RITUXIMAB			
- cost per pack	-	Average dispensed price per administration: $195.97 for Cycle 1 Day 1; $597.90 for Cycle 1 Day 2; $845.31 for Cycles 2-6	Weighted DPMA: $661.70[e]
- compliance	Average no. cycles: 5 67.1% pts received 6 cycles	6.03 scripts (1 administration on Cycle 1 Day 1; 1 on Cycle 1 Day 2; 4.03 for Cycles 2-6)[a]	4.98 scripts (6 scripts × 83.8% persistence × 99.1% dose intensity)[f]
- cost per course	-	$4,197	$3,294
Total cost per course	-	**$8,415**	**$8,314**

Source: Table 22, p80 of the CAPTIVATE CSR; Shanafelt 2019; 'I plus V - 1L CLL-SLL bilinks' spreadsheet provided with the submission; 'Utilisation cost workbook – ibrutinib FL CLL SLL fit FINAL' spreadsheet provided with the submission.

Abbreviations: DPMA, dispensed price for maximum amount; DPMQ, dispensed price for maximum quantity; FD, fixed duration; pts, patients

[a] Numbers of scripts per year in the economic model were derived from average treatment duration estimated individual patient data from CAPTIVATE AND ECOG1912, rounded up for each patient to the nearest whole number.

[b] Numbers of scripts per year for ibrutinib and venetoclax in the financial estimates were derived from the number of scripts required per patient per year (12.175) multiplied by the proportion of patients on treatment from time to treatment discontinuation Kaplan Meier curves; dose intensity based on individual patient data from CAPTIVATE.

[c] Estimated effective prices for initial and continuing venetoclax scripts based on the effective price of venetoclax in the R/R setting

[d] Average dispensed price per administration based on AEMP multiplied by number of vials per administration from ECOG1912 individual patient data with markups weighted based on 34.74%/65.25% public/private split derived from PBS dispensing data for rituximab January 2021 to March 2022

[e] Weighted DPMA based on 34.74%/65.25% public/private split derived from PBS dispensing data for rituximab January 2021 to March 2022

[f] Number of scripts per year for fludarabine, cyclophosphamide and rituximab in the financial estimates were derived from the maximum number of scripts (18 for fludarabine and cyclophosphamide; 6 for rituximab) multiplied by persistence (number of administrations/maximum administrations) and dose intensity derived from individual patient data from ECOG1912.

Estimated PBS usage & financial implications

6.65 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial impacts associated with the PBS listing of ibrutinib, for use in combination with venetoclax, for the treatment of patients with previously untreated CLL/SLL who would otherwise be suitable for fludarabine-based chemoimmunotherapy.

6.66 The sources of data used in the financial estimates are presented in Table 13.

Table 13: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Incident CLL patients	Incident CLL patients reported by AIHW (actual: 2011-2017; projected 2018-2021). Excel polynomial function used to extrapolate incident patient numbers over the initial six years of listing (2023 to 2028).	This appeared reasonable.
Incident SLL patients	SLL incidence reported by AIHW (2008-2012). Average SLL incidence for 2008-2012 for each 5-year age cohort used to derive incident patient numbers over the initial six years of listing (2023 to 2028).	Assumed no growth in SLL incidence from 2008-2012. It is unclear whether the incidence of SLL is increasing over time given the limited available incidence data for SLL.
Proportion fit for fludarabine-based chemoimmunotherapy	35%. Based on the July 2020 venetoclax resubmission, which assumed that 65% of patients were unsuitable for fludarabine-based chemoimmunotherapy.	The evaluation and the ESC considered that this proportion may be underestimated as some patients who are considered unsuitable for fludarabine-based chemoimmunotherapy may qualify for ibrutinib + venetoclax based on the proposed CIRS score and creatinine clearance criteria. The PBAC considered that in clinical practice, almost all patients would be unsuitable for fludarabine-based chemoimmunotherapy given FCR is poorly tolerated and associated with a risk of cytopenia and secondary malignancies.
Proportion of patients ever treated for CLL/SLL	74%. Based on the results of a 2021 survey of 30 haematologists commissioned by the sponsor. An estimated 32% of patients were considered to be fit, and of these patients, 26% were estimated to never receive treatment.	The proportion of 'fit' patients ever treated was considered to be uncertain, given that patients who are considered 'fit' may be reclassified as 'unfit' in later life.
Uptake of ibrutinib + venetoclax	Year 1: 70%; Years 2-6: 90%. Sponsor assumption, based on the uptake assumptions included for venetoclax in the July 2020 venetoclax resubmission and expert clinical opinion. In the pre-PBAC response, revised uptake rates were proposed: Year 1: 60%; Year 2: 75%; Year 3: 80%; Year 4: 85%; Years 5-6: 90%.	The evaluation considered that uptake may be overestimated given limited clinical evidence to support use of the regimen.
Ibrutinib scripts	First year: 11.13/patient; second year: 1.63/patient. Based on 12.175 scripts per year multiplied by the	It is unclear whether treatment persistence and adherence in the CAPTIVATE study will reflect

Parameter	Value applied and source	Comment
	average proportion of patients on treatment and dose intensity in the CAPTIVATE study.	persistence and adherence in Australian clinical practice.
Venetoclax scripts	First year: 1 starter pack script/patient + 7.51 continuing scripts/patient; second year: 2.19 continuing scripts/patient. Based on 12.175 scripts per year multiplied by the average proportion of patients on treatment and dose intensity in the CAPTIVATE study.	It is unclear whether treatment persistence and adherence in the CAPTIVATE study will reflect persistence and adherence in Australian clinical practice.
Fludarabine, cyclo-phosphamide and rituximab scripts	Fludarabine 13.74/patient; cyclophosphamide: 13.94/patient; rituximab: 4.98/patient. Based on assumed 6 cycles of FCR treatment, with rituximab administered intravenously on Day 0/1 of Cycles 1-6, and fludarabine and cyclophosphamide administered intravenously on Days 1-3 of each cycle. Treatment utilisation adjusted for persistence and dose intensity in the ECOG1912 trial.	It is unclear whether treatment persistence and adherence in the ECOG1912 trial will reflect persistence and adherence in Australian clinical practice.
Apixaban scripts	First year: 0.51/patient; second year: 0.08/patient. Based on 12.175 scripts per year multiplied by the average proportion of patients experiencing atrial fibrillation in the CAPTIVATE study (4.4%; 7/159), multiplied by the proportion of patients on ibrutinib treatment in the CAPTIVATE study.	Apixaban treatment was restricted to the period of ibrutinib treatment. However, anticoagulant therapy may be required beyond the ibrutinib treatment period. Patients may also require additional medications for the management of fibrillation (e.g., medications to control heart rate/rhythm).
Drug prices	Based on published prices for fludarabine, cyclophosphamide, fludarabine and apixaban. The effective price of venetoclax for previously untreated CLL/SLL was estimated based on the effective price of venetoclax in the R/R setting.	Drug costs for FCR were inappropriately derived based on the published DPMAs rather than the doses required for the FCR treatment regimen.
MBS costs	Included costs associated with the performance of an ECG at baseline for patients treated with ibrutinib (MBS Item 11723), and cost savings associated with a reduction in chemotherapy administrations (MBS Item 13950).	MBS costs were appropriately based on 80% of the schedule fee.

Source: Section 4, pp194-218 of the submission.

Abbreviations: AIHW, Australian Institute of Health and Welfare; CLL, chronic lymphocytic leukaemia; FCR, fludarabine + cyclophosphamide + rituximab; SLL, small lymphocytic lymphoma.

6.67 Table 14 presents the estimated net cost to the PBS/RPBS of listing ibrutinib + venetoclax.

Table 14: Estimated number of treated patients and the cost of ibrutinib + venetoclax to the PBS/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Total patients initiating IBR + VEN	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Number of IBR scripts	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Number of VEN scripts	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Estimated financial implications for ibrutinib + venetoclax						
Total cost of IBR	$[redacted][4]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]
Total cost of VEN	$[redacted][4]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]
Total cost of IBR + VEN	$[redacted][5]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][7]	$[redacted][7]
Estimated financial implications for other medicines						
Total saving to the PBS/RPBS[a]	$[redacted][8]	$[redacted][8]	$[redacted][8]	$[redacted][8]	$[redacted][8]	$[redacted][8]
Net financial implications						
Net cost to the PBS/RPBS	$[redacted][5]	$[redacted][9]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]
Net saving to MBS[b]	$[redacted][8]	$[redacted][8]	$[redacted][8]	$[redacted][8]	$[redacted][8]	$[redacted][8]
Net cost to PBS/RPBS + MBS	$[redacted][5]	$[redacted][9]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]
Pre-PBAC response						
Net cost to the PBS/RPBS	$[redacted][5]	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][6]	$[redacted][6]

Source: Financial impacts Excel workbook, Attachment 4.4 of the submission; and Financial impacts Excel workbook, pre-PBAC response.
Abbreviations: FCR, fludarabine + cyclophosphamide + rituximab; IBR, ibrutinib; MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme; VEN, venetoclax.

[a] Includes cost savings associated with displacement of fludarabine, cyclophosphamide and rituximab scripts, and additional costs associated with apixaban scripts for the management of atrial fibrillation.

[b] Includes cost savings associated with a reduction in chemotherapy administrations, and additional costs associated with a baseline ECG for patients treated with ibrutinib + venetoclax.

The redacted values correspond to the following ranges:
[1]< 500
[2]500 to < 5,000
[3]5,000 to < 10,000
[4]$10 million to < $20 million
[5]$20 million to < $30 million
[6]$40 million to < $50 million
[7]$50 million to < $60 million
[8]$0 to < $10 million
[9]$30 million to < $40 million

6.68 Based on the proposed effective price of ibrutinib and the estimated price of venetoclax, the submission estimated the net cost to the PBS/RPBS would be $20 million to < $30 million in Year 1 of listing, increasing to $40 million to < $50 million in Year 6, an estimated net cost of $200 million to < $300 million over the first six years of listing.

6.69 The pre-PBAC response proposed revised financial estimates which applied (a) lower uptake rates in Years 1 to 4; and (b) a 5% reduction in the ibrutinib price due to the 5-year statutory price reduction that is expected to be applied from 1 April 2023. In the pre-PBAC response, the estimated net cost to the PBS was $40 million to < $50 million in Year 6 and $200 million to < $300 million over the first six years of listing.

6.70 The evaluation and the ESC considered that the utilisation and financial impacts of listing ibrutinib + venetoclax were uncertain due to the following reasons:

- It is unclear whether the sponsor for venetoclax would agree to the proposed price of venetoclax for the new indication and any consequent changes to existing RSAs.

- The submission did not consider the impact of treatment with venetoclax + ibrutinib in the first-line setting on later-line treatment utilisation (refer to paragraphs 6.72 and 6.73).
- There may be potential for use outside of the intended restriction, including in patients who commence combination therapy but cease one component early in treatment.
- The ESC considered that the uptake rate was uncertain and may be overestimated given the limited clinical evidence to support use of the regimen and the adverse event profile. The pre-PBAC response provided revised financial estimates that applied lower uptake rates in Years 1 to 4, of 60% in Year 1 increasing to 90% in Year 5, however, the PBAC considered that the uptake potentially remained overestimated given the limited clinical data for use of ibrutinib + venetoclax.
- The proportion of patients who are considered suitable for ibrutinib + venetoclax may be underestimated given that some patients who are considered unsuitable for fludarabine-based chemoimmunotherapy may qualify for ibrutinib + venetoclax based on the proposed CIRS score and creatinine clearance criteria.

Quality Use of Medicines

6.71 The submission stated that patients, prescribers, and dispensers will be provided with appropriate education, resources, and support from the sponsor to promote appropriate prescribing and use of ibrutinib when used as a fixed duration treatment with venetoclax.

Financial Management – Risk Sharing Arrangements

6.72 Ibrutinib is currently included in an RSA for R/R CLL/SLL, which is a combined cap with venetoclax and acalabrutinib. Listing of ibrutinib + venetoclax in the first-line setting would be expected to reduce or delay later-line use of these treatments for R/R CLL/SLL. In its November 2019 consideration of ibrutinib for the first-line treatment of del17p patients, "the PBAC noted that the cost-effectiveness of ibrutinib in the first-line treatment of del17p patients relied on cost-offsets for ibrutinib and venetoclax as second- and third-line treatments. The PBAC advised that for these cost-offsets to be realised a combined RSA across the first-line and R/R settings was required" (paragraph 7.17, ibrutinib PSD, November 2019 PBAC Meeting). In this case, the ICER/QALY for ibrutinib is moderately sensitive to the inclusion of cost-offsets for subsequent line treatments (refer to paragraph 6.63), however the submission did not consider the impact of subsequent line treatments in the financial estimates, or an RSA proposal.

6.73 The PSCR stated 'as treatment with ibrutinib + venetoclax provides superior PFS over FCR, it is expected that the use of ibrutinib, venetoclax and acalabrutinib in the R/R CLL setting will be delayed as opposed to replaced (i.e., will not be a true offset) by the ibrutinib + venetoclax listing'. The ESC re-iterated its previous advice (for ibrutinib monotherapy in del17p patients) that, as the cost-effectiveness assessment includes

cost-offsets for ibrutinib and venetoclax as subsequent treatments (refer to paragraph 6.63), the impact of this should be considered in the financial estimates and RSA.

6.74 The pre-PBAC response proposed an RSA for ibrutinib (when used with venetoclax first-line in fit patients with CLL) based on the revised level of utilisation estimated in the pre-PBAC response with a rebate of | to apply for any use above the cap.

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

7 PBAC Outcome

7.1 The PBAC did not recommend ibrutinib, for use in combination with venetoclax, for the treatment of previously untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL). The PBAC considered the nominated comparator of fludarabine, cyclophosphamide and rituximab (FCR), although of historical relevance, is no longer the therapy most likely to be replaced in clinical practice given its limited use. The PBAC noted that, while the existing PBS restriction criteria define the patient populations on the basis of patient suitability for fludarabine-based chemoimmunotherapy, the advice from the clinical consultation was that these criteria are no longer relevant to clinical practice. The PBAC further noted that, based on the available evidence, it was not possible to determine the magnitude of clinical benefit with ibrutinib + venetoclax versus FCR due to the comparison being based on an unadjusted (naïve) comparison of single arms of different trials, and the limited follow-up of the ibrutinib + venetoclax (CAPTIVATE) trial. Overall, the PBAC considered the comparison presented in the submission versus FCR was not an informative basis for the listing of ibrutinib + venetoclax.

7.2 The PBAC noted the input from individuals, health professionals and organisations regarding the high clinical need for alternative treatments for CLL/SLL in the first-line setting. The PBAC considered that it would be ideal to have a range of first-line subsidised treatment options available to patients, with treatment able to be tailored to the needs of an individual patient. Factors considered could include co-existing disease, the extent of lymph node involvement, the goals of treatment, a preference for fixed duration or continuous treatment, and the acceptability of an initial period of intravenous treatment. The PBAC noted advice from the clinician consultation that there are a lack of clinical trial data available to differentiate between regimens or determine which particular regimen would be preferable in a particular patient group/setting.

7.3 The PBAC noted that the restrictions for venetoclax + obinutuzumab in first-line CLL/SLL require patients to be inappropriate for fludarabine based chemoimmunotherapy and have a cumulative illness rating scale (CIRS) score > 6 (excluding CLL-induced illness or organ damage) or a creatinine clearance < 70 mL/min, and that the complement of each had been proposed for inclusion in the ibrutinib + venetoclax restrictions (i.e. CIRS ≤6 and creatinine clearance ≥ 70 mL/min). However, the PBAC considered that it was no longer clinically relevant to include the

CIRS score in restrictions for first-line CLL/SLL therapies given it was developed to assess the ability of a patient to tolerate chemoimmunotherapy and was less relevant for targeted agents. The PBAC considered that, rather than relying on the CIRS score and/or creatinine clearance < 70 mL/min, it would be more clinically appropriate for clinicians/patients to decide the most appropriate treatment regimen for a particular patient, which may involve consideration of a broader range of factors including biological characteristics of the disease and an individual's specific organ sensitivities (e.g. cardiac or renal risk). The PBAC noted that there is clinical evidence for ibrutinib + venetoclax in less fit patients (those aged 65 years or older and/or with comorbidities) and that this evidence (a randomised, open-label, Phase 3 study versus chlorambucil + obinutuzumab) was included in the application to the TGA.

7.4 The submission nominated FCR as the main comparator as it is the only PBS-listed treatment for the requested population. The PBAC acknowledged that the existing PBS criteria in the first-line CLL/SLL restrictions define the patient populations on the basis of 'inappropriate for fludarabine-based chemoimmunotherapy', and in the relapsed/refractory CLL/SLL restrictions on the basis of 'unsuitable for treatment with a purine analogue'. However the PBAC agreed with the ESC and the expert advice received at the clinician consultation (paragraphs 4.8 and 6.3) that these criteria are no longer relevant to clinical practice as almost all patients are 'inappropriate for fludarabine-based chemoimmunotherapy' given FCR is poorly tolerated and associated with a risk of cytopenia and secondary malignancies. The PBAC noted that FCR is no longer a preferred regimen in any patient group and is no longer commonly used in clinical practice. The PBAC therefore considered that FCR is no longer the therapy most likely to be replaced in clinical practice and its usefulness as a comparator was limited.

7.5 The PBAC noted that the comparative efficacy of ibrutinib + venetoclax versus FCR was based on an unanchored, unadjusted indirect treatment comparison of the fixed duration cohort of CAPTIVATE (ibrutinib + venetoclax) and the FCR arm of ECOG1912. The PBAC considered that, while the estimated hazard ratios for progression-free survival and overall survival appeared highly favourable towards ibrutinib + venetoclax, the magnitude of the benefit was highly uncertain due to the naïve nature of the comparison as well as:

- The follow-up data for ibrutinib + venetoclax from CAPTIVATE were immature in the context of an indolent condition and the unknown long-term benefit following a fixed duration regimen with a maximum of 15 cycles of treatment. The PBAC noted with a median follow-up of 38.7 months there were only a small number of PFS events (28) and OS events (3). Overall, the PBAC considered any incremental benefit in terms of progression-free or overall survival was not able to be quantified, and that a longer duration of follow-up from the CAPTIVATE study, which the PSCR stated is expected in late 2023, may help to determine the magnitude of the clinical benefit in terms of PFS with fixed duration ibrutinib + venetoclax.

- No statistical adjustments were conducted to account for differences in study population or circumstances of use. The PBAC considered this approach inherently underestimated the statistical uncertainty associated with other unknown confounders.
- The PBAC considered that it was unclear whether the combination of ibrutinib + venetoclax offers a superior risk-benefit profile compared with single agent ibrutinib or venetoclax in the first-line setting, and that the contribution of each medicine to the combined treatment effect was unclear. In particular, the PBAC considered the benefit of ibrutinib + venetoclax (fixed duration) versus internationally accepted current standard treatments such as BTKi monotherapy (treat to progression) is unclear.
- 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 re-treated with single-agent ibrutinib following disease progression.

7.6 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".

7.7 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. The submission's extrapolation of the naïve comparison of PFS curves resulted in large differences between treatment arms over the 20-year time horizon, which may not be realised in clinical practice.

7.8 The submission and PSCR indicated that, given the immaturity of the overall survival data from CAPTIVATE, a more traditional partitioned survival model could not be developed. Instead, a two-state model structure (progression-free and a combined progressed/dead state) was used in which patients who progressed were assigned costs and outcomes based on the results of the model for ibrutinib in the R/R setting. The PBAC considered it was unclear whether the health outcomes associated with ibrutinib in the BTK inhibitor-naïve R/R setting of the ibrutinib R/R model will be the same as the proposed population of patients who would already have been treated with ibrutinib + venetoclax. The PBAC further noted that none of the parametric models appeared to be a good visual fit for the ibrutinib + venetoclax Kaplan Meier data.

7.9 The PBAC noted that the submission used an epidemiological approach to estimate the use and financial implications of listing ibrutinib + venetoclax on the PBS. The PBAC noted that the estimated number of patients for which treatment with ibrutinib + venetoclax was assumed to replace FCR far exceeded the current use of FCR (500 to < 5,000 patients in Year 6 versus less than 150 patients, per Table 14 and paragraph 4.9).

The PBAC considered that this discrepancy reflected that FCR is no longer the appropriate main comparator. The PBAC noted the revised financial estimates presented in the pre-PBAC response had applied a lower uptake rate but considered that the uptake potentially remained overestimated given the limited clinical data for use of ibrutinib + venetoclax, and further that the financial estimates remained uncertain as outlined in paragraph 6.70 and 6.73.

7.10 The PBAC considered a resubmission for ibrutinib + venetoclax should address the following issues:

- The proposed PBS restriction criteria, noting the PBAC advice in paragraph 7.13 below regarding revisions to the existing CLL/SLL PBS restrictions.
- The appropriate main comparator, noting the PBAC advice in paragraph 7.13 regarding revisions to the existing CLL/SLL PBS restrictions. Should venetoclax + obinutuzumab be listed for all patients regardless of suitability for fludarabine-based chemoimmunotherapy and regardless of CIRS score, the PBAC noted that there may be a degree of overlap with the likely patient population for ibrutinib + venetoclax.
- The 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.
- The PBAC noted the proposed restrictions and comparator in any resubmission will inform the approach for the economic model and financial forecasts. However, the PBAC also noted that the economic model informing the PBS listing for venetoclax + obinutuzumab for the first-line treatment of CLL/SLL was based on a randomised head-to-head trial versus the accepted comparator (chlorambucil + obinutuzumab) and hence the pricing was informed by relatively robust data. On this basis and given the potential overlap in the patient populations treated with venetoclax + ibrutinib and venetoclax + obinutuzumab, the PBAC considered a cost comparison of the two regimens would be informative in any resubmission.

7.11 The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

7.12 The PBAC noted that this submission is eligible for an Independent Review.

7.13 Based on the advice received as part of the clinical consultation held on 1 December 2022 (paragraph 6.3) the PBAC advised that the existing PBS criteria for CLL/SLL treatments be amended as follows:

- The venetoclax + obinutuzumab restrictions for first-line CLL/SLL should be updated to remove the criterion 'inappropriate for fludarabine-based chemoimmunotherapy' and remove reference to the requirement for patients to have a CIRS score > 6 or creatinine clearance < 70 mL/min given the CIRS score was designed to predict toxicity with chemoimmunotherapy rather than targeted

agents.

- The requirement for patients to be considered unsuitable for treatment or retreatment with a purine analogue should be removed from the restrictions for all PBS listed drugs for CLL/SLL in the relapsed or refractory setting. The PBAC noted this would remove the notes defining this criterion (which include criteria around factors like age and/or CIRS score and del17p).

Outcome:
Not recommended

8 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.

9 Sponsor's Comment

The sponsor had no comment.