

**6.05 VENETOCLAX,
Tablet, 10 mg, 50 mg, 100 mg,
Venclexta[®],
AbbVie Pty Ltd.**

1 Purpose of submission

- 1.1 The submission requested a Section 85 (General Schedule), Authority Required (Streamlined) listing for venetoclax in combination with obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL) in patients with coexisting conditions who are inappropriate for fludarabine based chemo-immunotherapy.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus obinutuzumab in combination with chlorambucil. The PBAC has not previously considered venetoclax for this restriction.

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

Component	Description
Population	Patients with previously untreated chronic lymphocytic leukaemia and coexisting conditions, inappropriate for fludarabine based chemo-immunotherapy
Intervention	Venetoclax (12 cycles over 12 months, oral tablets) with dose up-titration over the first 5 weeks, in combination with obinutuzumab (6 cycles over 6 months, intravenous infusion)
Comparator	Main comparator: Chlorambucil + obinutuzumab, (6 cycles obinutuzumab, intravenous infusion; 6 cycles chlorambucil; oral tablets) ^a
Outcomes	Improved progression free survival and increased time to next anti-CLL treatment
Clinical claims	Venetoclax + obinutuzumab is superior in efficacy to chlorambucil + obinutuzumab Venetoclax + obinutuzumab is non-inferior in safety compared to chlorambucil + obinutuzumab

Source: Table 1, p.3 of the submission

Abbreviations: CLL, chronic lymphocytic leukaemia

^a Chlorambucil was administered for 12 cycles in the key clinical trial supporting the submission

2 Background

Registration status

- 2.1 The submission was a parallel process application for expansion of the current venetoclax TGA approved indication to “the treatment of adult patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)”. The ‘dose and method of administration’ section in the draft PI specifies use in combination with obinutuzumab for first line CLL/SLL. At the time of evaluation for PBAC consideration, the TGA delegate’s first round report was available, and provided with the submission. The TGA delegate’s summary was received prior to the PBAC meeting.
- 2.2 Venetoclax is currently registered on the ARTG as monotherapy for relapsed/refractory CLL with 17p deletion, or when there are no other suitable treatment options, and as combination therapy with rituximab for relapsed/refractory CLL.

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- 2.3 Venetoclax was approved by the US Food and Drug Administration (FDA) on 15 May 2019 for adult patients with previously untreated CLL/SLL, and is currently being considered for registration in the European Union (EU), Canada, Switzerland and New Zealand.

Previous PBAC consideration

- 2.4 Venetoclax is currently listed on the PBS as combination therapy with rituximab (following venetoclax dose titration) for the treatment of relapsed/refractory CLL in patients unsuitable for treatment or retreatment with a purine analogue, on a cost-minimisation basis versus ibrutinib monotherapy.

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

3 Requested listing

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

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer	
VENETOCLAX (STARTING PACK) venetoclax 10 mg tablet [14] (& venetoclax 50 mg tablet [7] (& venetoclax 100 mg tablet [7] (& venetoclax 100 mg tablet [14], 1 pack	11630D	1	1	0	Venclexta®	AbbVie Pty Ltd

Category/Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction level/ Method:	<input type="checkbox"/> Unrestricted benefit <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Authority Required – Streamlined
Episodicity:	[iii] Untreated
Severity:	Previously untreated
Condition:	Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Indication:	Previously untreated chronic lymphocytic leukaemia in patients with coexisting conditions who are inappropriate for fludarabine based chemo immunotherapy. Untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Treatment Phase:	Initial treatment in first-line therapy – Does titration (ramp-up)

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Clinical criteria:	<p>The condition must be previously untreated AND Patient must be inappropriate for fludarabine based chemo-immunotherapy AND The treatment must be in combination with obinutuzumab for this condition AND Patient must have a creatinine clearance 30 mL/min or greater AND Patient must have a total cumulative illness rating scale (CIRS) score of greater than 6 (excluding CLL-induced illness or organ damage); OR Patient must have a creatinine clearance less than 70 mL/min. AND Treatment must be discontinued in patients who experience disease progression whilst on this treatment. The treatment must be ceased upon disease progression or after completion of 12 cycles of PBS-subsidised treatment with this drug for this condition, whichever comes first.</p>
Administrative Advice:	<p>No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.</p>

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Proprietary Name and Manufacturer
VENETOCLAX (CONTINUING TREATMENT) venetoclax 100 mg tablet, 120	NEW	1	120	5 4	Venclexta® AbbVie Pty Ltd

Category/Program:	GENERAL – General Schedule (Code GE)
Prescriber type	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction level/ Method:	<input type="checkbox"/> Unrestricted benefit <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Authority Required – Streamlined
Episodicity:	[nil]
Severity:	Previously untreated
Condition:	Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Indication:	Previously untreated chronic lymphocytic leukaemia in patients with coexisting conditions who are inappropriate for fludarabine based chemo-immunotherapy Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Treatment Phase:	First Continuing treatment (treatment cycles 2 to 6 inclusive) of first-line therapy
Clinical criteria:	<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition AND The treatment must be in combination with obinutuzumab (refer to Product Information for timing of obinutuzumab) for the first six cycles, followed by venetoclax monotherapy.</p>
Prescriber instructions:	<p>Treatment must be ceased in patients who experience disease progression while on this treatment. The treatment must be ceased upon disease progression.</p>
Administrative Advice:	<p>No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.</p>

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Proprietary Name and Manufacturer
VENETOCLAX venetoclax 100 mg tablet, 120	NEW	1	120	5	Venclexta® AbbVie Pty Ltd

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Category/Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction level/ Method:	<input type="checkbox"/> Unrestricted benefit <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Authority Required – Streamlined
Episodicity:	[nil]
Severity:	[nil]
Condition:	Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Indication:	Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Treatment Phase:	Second continuing treatment (treatment cycles 7 to 12 inclusive) of first-line therapy
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition
Prescriber instruction:	The treatment must be ceased upon disease progression or after completion of 12 cycles of PBS-subsidised treatment with this drug for this condition, whichever comes first.
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

3.2 Instead of having a new, separate ‘extension of dose titration’ restriction, the Secretariat proposed modifying the existing venetoclax extension of dose titration listing. The amended restriction will allow use as monotherapy or in combination with chlorambucil.

Category/Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction level/ Method:	<input type="checkbox"/> Unrestricted benefit <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Authority Required – Streamlined
Episodicity:	[nil]
Severity:	Previously untreated
Condition:	Chronic lymphocytic leukaemia
Indication:	Previously untreated chronic lymphocytic leukaemia in patients with coexisting conditions who are inappropriate for fludarabine-based chemo-immunotherapy
Treatment Phase:	Initial treatment – extension dose ramp-up
Clinical criteria:	Patient must have experienced a treatment interruption during PBS-subsidised dose ramp-up with this drug for this condition AND Patient must not develop disease progression while being treated with PBS-subsidised treatment with this drug for this condition AND The treatment must be in combination with obinutuzumab for this condition
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

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Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer	
VENETOCLAX (DOSE HOLD PACK)						
venetoclax 10 mg tablet, 14	11624T	1	14	0	Venclexta®	AbbVie Pty Ltd
venetoclax 50 mg tablet, 7	11648C	1	7	0		

Indication:	Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Treatment phase:	Initial treatment – Extension of dose titration – Dose modification requirement
Clinical criteria:	<p>Patient must have experienced a treatment interruption during the PBS subsidised dose titration with this drug for this condition</p> <p>The treatment must be for dose titration purposes</p> <p>AND</p> <p>Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition</p> <p>AND</p> <p>The treatment must be used as monotherapy for this condition under this restriction</p>
Administrative Advice:	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>

- 3.3 The submission requested a Special Pricing Arrangement (SPA) as there are SPAs currently in place for PBS listed venetoclax in relapsed/refractory CLL and obinutuzumab in the first line treatment of CLL.
- 3.4 The requested published and effective prices for venetoclax are [REDACTED].
- 3.5 The requested restriction is narrower than the proposed TGA indication, and restricts subsidised venetoclax use in first-line treatment of CLL to combination therapy with obinutuzumab in patients inappropriate for fludarabine based chemo-immunotherapy, with a creatinine clearance of ≥ 30 mL/min, and a total cumulative illness rating scale (CIRS) score of > 6 or a creatinine clearance < 70 mL/min. Although the proposed TGA indication includes CLL and SLL, the proposed PBS listing specifies CLL only. The PBAC noted that CLL and SLL are essentially the same disease, and therefore considered that the indication should be amended to include SLL.
- 3.6 The requested restriction describes a different but overlapping population to the ibrutinib restriction recommended by the PBAC at the November 2019 meeting (i.e. treatment naïve CLL/SLL patients with del(17p); Ibrutinib PSD, November 2019), as it includes, but is not limited to, patients with the del(17p) cytogenetic aberration, requires coexisting conditions, and excludes patients with SLL.
- 3.7 The requested restriction is based on the current obinutuzumab PBS listing for previously untreated CD20 positive CLL (PBS item 10407R) in combination with chlorambucil, but includes a broader population not limited to CD20 positive patients. As venetoclax is used in combination with obinutuzumab and the obinutuzumab restriction limits use to CD20 positive patients, it is expected that venetoclax + obinutuzumab use will be restricted to patients who are CD20 positive. The ESC

considered this to be appropriate, noting the majority of patients with CLL are CD20 positive. The submission requested amendment of the current PBS listing for obinutuzumab to allow use in combination with venetoclax. The PBAC considered that, if recommended, flow-on changes to the current listings for obinutuzumab to allow use with venetoclax would be required. The PBAC also advised that flow on changes would be required for the venetoclax listings in the relapsed or refractory setting to restrict use of venetoclax to one course per lifetime.

- 3.8 The clinical criterion “patient must be inappropriate for fludarabine based chemo-immunotherapy” is consistent with the PBS restriction for obinutuzumab in first line CLL, but is not explicitly defined in the restriction. It is unclear how the population considered inappropriate for fludarabine based chemo-immunotherapy will be identified in clinical practice. Consistent with previous considerations to list ofatumumab and obinutuzumab for first-line CLL, the PBAC did not propose a definition.
- 3.9 The draft Product Information recommends that venetoclax + obinutuzumab is administered for a finite duration (12 cycles/months) or ceased upon disease progression. The PBAC therefore considered that limiting treatment to 12 months treatment or cessation of treatment upon disease progression (whichever comes first) in the second continuing restriction would be appropriate.

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

4 Population and disease

- 4.1 Chronic lymphocytic leukaemia is a slow progressing blood cancer (five year relative survival from diagnosis 77.9%) characterised by the proliferation of functionally incompetent B-lymphocytes in the blood, bone marrow, lymph nodes, spleen and liver. CLL is more common in males (65%) and the elderly (mean age at diagnosis in Australia is 70 years; Cancer in Australia 2017, Australian Institute of Health and Welfare).
- 4.2 The CLL disease trajectory is highly heterogeneous and prognosis depends on disease characteristics (staging at diagnosis, cytogenetics, complications), treatment response (tolerance, relapse) and patient characteristics (age at diagnosis, comorbidities). Patients with the genetic aberrations TP53 mutation, del(17p) and unmutated IGVH status generally exhibit poor prognosis and are more likely to require targeted treatment.
- 4.3 The clinical management algorithm positions venetoclax + obinutuzumab as an alternative to chlorambucil + obinutuzumab, rituximab + chlorambucil and chlorambucil for previously untreated CLL in patients inappropriate for purine

analogue chemotherapies. The ESC noted recent clinical management guidelines¹ recommend first-line ibrutinib in patients with del(17p) or TP53 mutation, which was recommended by the PBAC in November 2019.

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

5 Comparator

- 5.1 The submission nominated chlorambucil + obinutuzumab as the main comparator. Obinutuzumab is listed on the PBS as a first-line treatment in combination with chlorambucil for CLL patients with comorbidities who are inappropriate for fludarabine based chemo-immunotherapy, and was the preferred subsidised therapy for first-line treatment of CLL in unfit patients (para 5.1, Ibrutinib PSD, November 2017). The PBAC previously considered chlorambucil + obinutuzumab to be the appropriate main comparator for this population when considering first-line therapy with ibrutinib in November 2017 (para 5.2, Ibrutinib PSD, November 2017).
- 5.2 The submission identified ibrutinib in combination with obinutuzumab as a potential near market comparator for first-line treatment of CLL. The PBAC recommended ibrutinib (monotherapy) for patients with previously untreated CLL/SLL with evidence of one or more 17p deletions at the November 2019 meeting on the basis of the results of the iLLUMINATE trial (ibrutinib + obinutuzumab versus chlorambucil + obinutuzumab), recognising the high clinical need for effective treatments in the 17p deletion population (PBAC Outcomes, November 2019). The evaluation considered ibrutinib (monotherapy) to be an appropriate comparator in patients with del(17p). Given that ibrutinib + obinutuzumab is not available in Australia for first-line treatment of CLL, the ESC agreed with the Pre-Sub-Committee Response (PSCR) that the near market comparison was not relevant for this submission.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the progression of CLL/SLL and informed the PBAC that earlier use of targeted agents is preferable as depth of remission is considered a predictor of survival. The clinician responded to the Committee's questions regarding the key trial, CLL-14 and the differences in post-progression treatment patterns. The clinician speculated that the differences in time to next treatment (TTNT) observed across treatment arms in the key trial may have

¹ iwCLL guidelines (Feb 2020), NCCN guidelines (2019)_and ESMO guidelines (2017)

been due to the small number of early progression event in the venetoclax + obinutuzumab arm being shallow remissions and hence, next treatments were administered earlier than was seen in the chlorambucil + obinutuzumab arm.

- 6.2 The PBAC considered the hearing was informative for providing context about the post-progression treatment patterns observed in the CLL-14 trial.

Consumer comments

- 6.3 The PBAC noted and welcomed the input from individuals (8) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described benefits of treatment with the targeted combination therapy of venetoclax + obinutuzumab, including the option of avoiding treatment/re-treatment with fludarabine based chemotherapy when not clinically appropriate, as well as improved quality of life, higher rates of remission, and a superior side effect profile versus the alternative initial therapies (i.e. fludarabine based chemotherapy and chlorambucil + obinutuzumab). The PBAC did not consider superior safety to chlorambucil + obinutuzumab was demonstrated in the CLL-14 trial.
- 6.4 The PBAC noted the support received from the Leukaemia Foundation, Lymphoma Australia, and Rare Cancers Australia detailing the superior progression free survival (PFS) time for venetoclax + obinutuzumab (versus chlorambucil + obinutuzumab) in the first-line setting, with the benefit of a fixed treatment duration, as well as the unmet need for treatment options in CLL patients who are unable to tolerate the current standard of care.

Clinical trials

- 6.5 The submission was based on one head-to-head randomised open label trial comparing venetoclax + obinutuzumab to chlorambucil + obinutuzumab (Trial CLL-14).
- 6.6 Details of the CLL-14 trial are provided in the table below.

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Table 2: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Venetoclax		
CLL-14 (NCT02242942)	A prospective, open-label, multicenter randomized Phase III trial to compare the efficacy and safety of a combined regimen of obinutuzumab and venetoclax (GDC-0199/ABT 199) versus obinutuzumab and chlorambucil in previously untreated patients with CLL and coexisting medical conditions Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions Fischer K, Al-Sawaf O, Bahlo J, et al. Effect of fixed-duration venetoclax plus obinutuzumab (VTX+Obi) on progression free survival (PFS), and rates and duration of minimal residual disease negativity (MRD-) in previously untreated patients (pts) with chronic lymphocytic leukemia (CLL) and comorbidities	February 2019 <i>New England Journal of Medicine</i> 2019; 380(23): 2225-2236 <i>Journal of Clinical Oncology</i> 2019; 37:abstract 7502

Source: Table 17, pp.27-28 of the submission

6.7 The key features of the CLL-14 randomised trial are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Venetoclax + obinutuzumab versus chlorambucil + obinutuzumab						
CLL-14	432	R, OL, MC, Phase III (median follow-up 29.06 months ^a)	Unclear	Previously untreated adults with CLL; and CIRS score > 6 or CrCL < 70 mL/min	Primary PFS (INV), ^b Secondary PFS (IRC), OS, TTNT, MRD negativity, ORR, CR, QoL,	INV assessed PFS, OS, TTNT

Source: Table 19, p.31 of the submission; Table 4, Attachment 4 to the submission

Abbreviations: CCL, chronic lymphocytic leukaemia; CIRS, cumulative illness rating scale; CR, complete response; CrCl, creatinine clearance; INV, investigator; IRC, independent review committee; MC, multi-centre; MRD, minimal residual disease; OL, open label; ORR, overall response rate; OS, overall survival; PFS, progression free survival; QoL, quality of life; R, randomised; SLL, small lymphocytic lymphoma; TTNT, time to next anti-CLL treatment

^a Median follow-up ITT population = 29.06 months; venetoclax + obinutuzumab = 28.79 months; chlorambucil + obinutuzumab = 29.24 months

^b Investigator assessed PFS (unblinded) was the pre-specified primary outcome of CLL-14, but IRC assessed PFS was nominated as the primary outcome for the US Federal and Drug Administration regulatory review

6.8 The PBAC agreed with the ESC and considered that the use of unblinded investigator assessed outcomes in the CLL-14 trial was associated with a high risk of bias in the primary and key secondary outcomes (PFS, TTNT, response to treatment). However, the PBAC noted that although outcomes assessed by an independent review committee (IRC) may be preferred, they demonstrated similar results to investigator assessed PFS. In both assessments, knowledge of treatment allocation may have led to differences in management between treatment arms, as well as biased reporting of adverse events.

6.9 The ESC noted that in the CLL-14 trial, baseline characteristics were generally similar between treatment arms, except for the proportion of patients with a CIRS score ≤ 6 at baseline (venetoclax + obinutuzumab 13.9%; chlorambucil + obinutuzumab 18.1%), which suggested that there were more patients in the venetoclax + obinutuzumab arm with a high number of comorbidities.

Comparative effectiveness

Direct comparison (venetoclax + obinutuzumab vs chlorambucil + obinutuzumab)

6.10 The submission was based on CLL-14 trial data with a data cut-off date of 17 August 2018 (median follow-up of 29.06 months). The sponsor subsequently provided updated data for the CLL-14 trial with a later data cut-off of 23 August 2019 (median follow-up not reported). Results for both data cut-offs are presented where available.

6.11 Results of the direct comparison between venetoclax + obinutuzumab versus chlorambucil + obinutuzumab for PFS are presented in Table 4, with Kaplan-Meier plots for investigator assessed PFS for the August 2018 cut-off presented in Figure 1.

Table 4: Results of PFS for CLL-14 (ITT)

	INV assessed PFS		IRC assessed PFS	
	Venetoclax + obinutuzumab	Chlorambucil + obinutuzumab	Venetoclax + obinutuzumab	Chlorambucil + obinutuzumab
N	216	216	216	216
PFS; data cut-off 17 August 2018				
Patients with events, n (%)	30 (13.9%)	77 (35.6%)	29 (13.4%)	79 (36.6%)
Disease progression, n (%)	14 (6.5%)	69 (31.9%)	14 (6.5%)	71 (32.9%)
Death any cause, n (%)	16 (7.4%)	8 (3.7%)	15 (6.9%)	8 (3.7%)
Median time to event, months (95% CI)	NE (NE)	NE (31.1, NE)	NE (NE)	NE (31.1, NE)
Stratified HR (95% CI) ^a	0.35 (0.23, 0.53)		0.33 (0.22, 0.51)	
Estimated 1 year PFS rate, % (95% CI)	n=192 94.6% (91.5, 97.7)	n=184 92.1% (88.4, 95.8)	n=192 94.6% (91.5, 97.7)	n=183 91.2% (87.3, 95.1)
Estimated 2 year PFS rate, % (95% CI)	n=153 88.2% (83.7, 92.6)	n=110 64.1% (57.4, 70.8)	n=148 88.6% (94.2, 93.0)	n=108 63.7% (57.0, 70.4)
Updated PFS; data cut-off 23 August 2019				
Patients with events, n (%)	42 (19.4%)	113 (52.3%)	NR	NR
Disease progression, n (%)	21 (9.7%)	102 (47.2%)		
Death any cause, n (%)	21 (9.7%)	11 (5.1%)		
Median time to event, months (95% CI)	NR	35.6 (33.7, 40.7)		
Stratified HR (95% CI) ^a	0.31 (0.22, 0.44)			
Estimated 1 year PFS rate, % (95% CI)	n=192 94.6% (91.5, 97.7)	n=184 92.1% (88.4, 95.8)	NR	NR
Estimated 2 year PFS rate, % (95% CI)	n=176 88.2% (83.7, 92.6)	n=129 64.6% (58.0, 71.2)		
Estimated 3 year PFS rate, % (95% CI)	n=97 81.9% (76.5, 87.3)	n=69 49.5% (42.4, 56.6)		

Source: Table 31, p.59 of the submission; Tables 20 and 21, p.106-108 of the CLL-14 Clinical Study Report; Table 1, p.2 of VTX_PBAC submission_updated data.docx

Abbreviations: CI, confidence interval; HR, hazard ratio; INV, investigator assessed result; IRC, independent review committee; ITT, intention-to-treat; NE, not estimable; NR, not reported; PFS, progression free survival

^a Hazard ratio < 1 favours venetoclax + obinutuzumab; statistically significant results in bold

Table 5: Results of OS from CLL-14 (ITT)

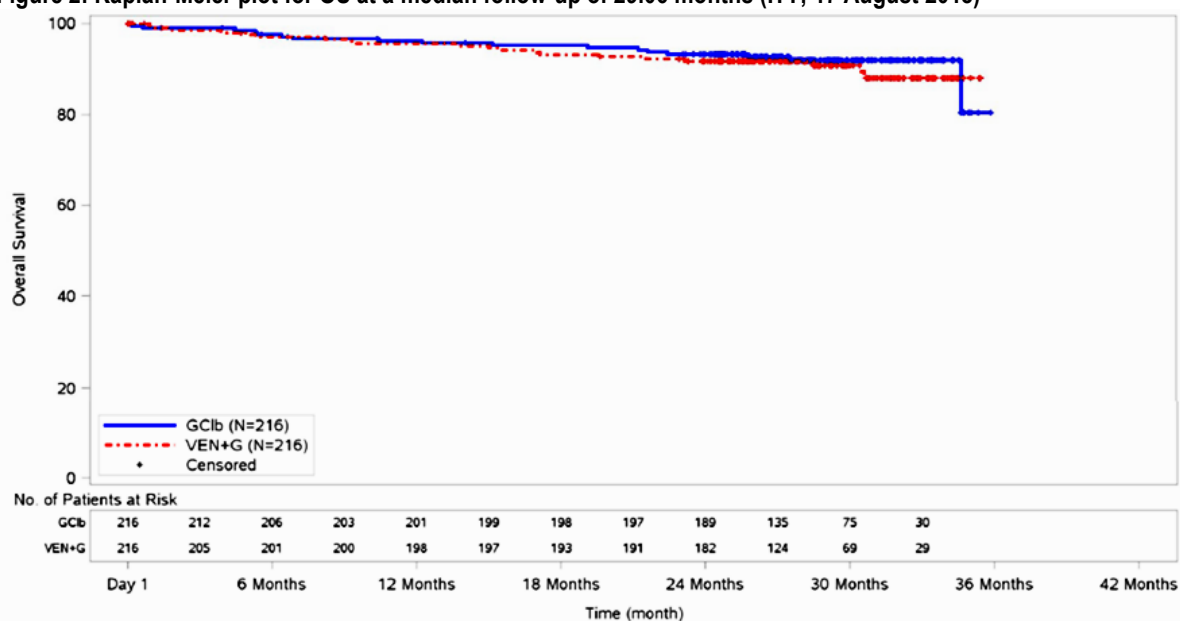
	Venetoclax + obinutuzumab	Chlorambucil + obinutuzumab
N	216	216
Overall survival; data cut-off 17 August 2018		
Patients with events, n (%)	20 (9.3%)	17 (7.9%)
Median time to event, months (95% CI)	NE (0, 35.4)	NE (0, 35.4)
Stratified HR (95% CI) ^a	1.24 (0.64, 2.40)	
Estimated 1 year OS rate, % (95% CI)	93.3% (89.8, 96.7)	95.3% (92.4, 98.1)
Estimated 2 year OS rate, % (95% CI)	91.8% (88.1, 95.5)	93.3% (90.0, 96.7)
Updated overall survival; data cut-off 23 August 2019		
Patients with events, n (%)	27 (12.5%)	27 (12.5%)
Median time to event, months (95% CI)	NE	NE
Stratified HR (95% CI) ^a	1.03 (0.60, 1.75)	
Estimated 2 year OS rate, % (95% CI)	91.8% (88.1, 95.5)	93.3% (90.0, 96.7)
Estimated 3 year OS rate, % (95% CI)	88.9% (84.6, 93.1)	88.0% (83.6, 92.4)

Source: Table 33, p.63 of the submission; Table 4, p.5 of VTX_PBAC submission_updated data.docx; Table, p.1 of response-s31-qu8- efficacy.pdf

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NE, not estimable; OS, overall survival

^a Hazard ratio < 1 favours venetoclax + obinutuzumab

Figure 2: Kaplan-Meier plot for OS at a median follow-up of 29.06 months (ITT; 17 August 2018)



Source: Figure 11, p.136 of the CLL-14 Clinical Study Report

Abbreviations: CI, confidence interval; IRC, independent review committee; ITT, intention-to-treat; GClb, chlorambucil + obinutuzumab; PFS, progression free survival; VEN+G, venetoclax + obinutuzumab

Note: Censored for surviving patients at last disease assessment

- 6.16 There was no statistically significant difference in OS between patients treated with venetoclax + obinutuzumab versus chlorambucil + obinutuzumab, at a median follow up of 29.06 months. Median OS was not reached in either treatment arm.
- 6.17 Updated CLL-14 data from the August 2019 cut-off showed no statistically significant difference in OS between treatments. Venetoclax + obinutuzumab showed no additional benefit in terms of OS compared to chlorambucil + obinutuzumab. The PBAC agreed with the ESC that OS was not an informative outcome due to

downstream effective treatments and the older mean age at diagnosis (70 years), i.e. patients may die of other causes.

6.18 Results of the direct comparison for time to next anti-CLL treatment (TTNT) are presented in Table 6, with Kaplan-Meier plots for the August 2019 cut-off presented in Figure 3.

Table 6: Time to next anti-CLL treatment for CLL-14 (ITT)

	Venetoclax + obinutuzumab	Chlorambucil + obinutuzumab
N		
Time to next anti-CLL treatment (17 August 2018)		
Patients with event ^a , n (%)		
New anti-leukemic treatment, n (%)		
Death, n (%)		
Median time to treatment event, months (95% CI)	NE (NE)	NE (, NE)
Stratified hazard ratio, (95% CI) ^a		
TTNT event free rate at 1 year, % (95% CI)	n= % (,)	n= % (,)
TTNT event free rate at 2 years, % (95% CI)	n= % (,)	n= % (,)
Updated time to next anti-CLL treatment (23 August 2019)		
Patients with event ^a , n (%)		
New anti-leukemic treatment, n (%)		
Death any cause, n (%)		
Median time to treatment event, months (95% CI)	NR	NR
Stratified hazard ratio, (95% CI) ^b		
TTNT event free rate at 1 year, % (95% CI)	n= % (,)	n= % (,)
TTNT event free rate at 2 years, % (95% CI)	n= % (,)	n= % (,)
TTNT event free rate at 3 years, % (95% CI)	n= % (,)	n= % (,)

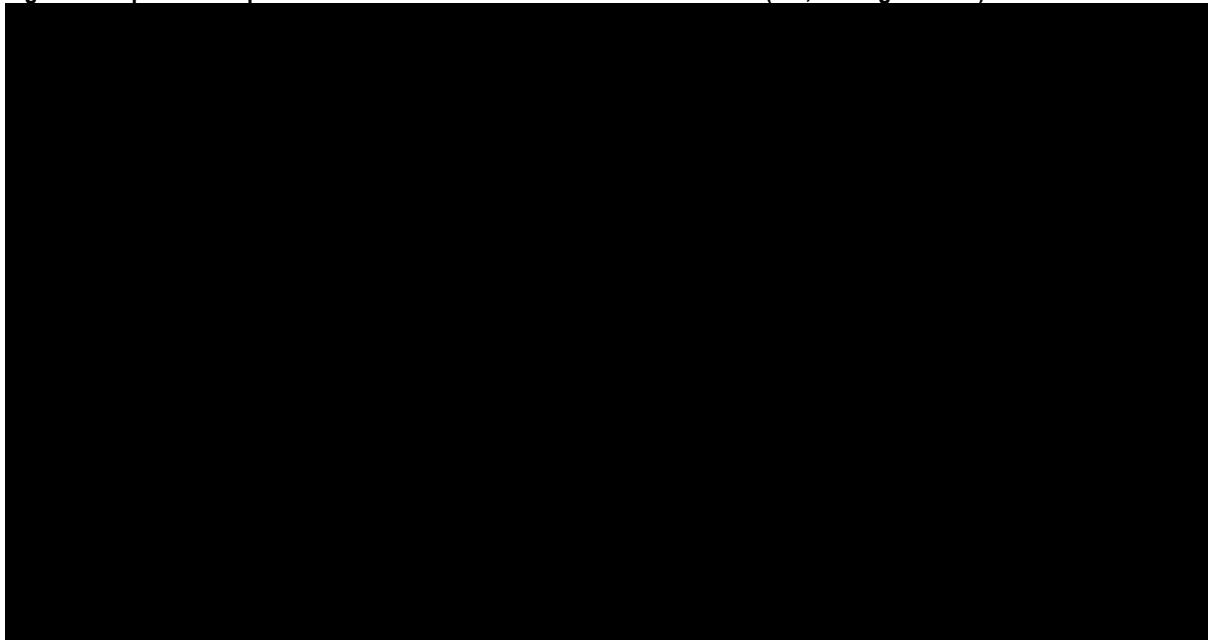
Source: Table 38, p.72 of the submission; Table 3, p.3 of VTX_PBAC submission_updated data.docx; p.2 of t_ef_tte_TTNTINV_NSFRFL_323_IT.pdf

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukaemia; ITT, intention-to-treat; NE, not estimable; NR, not reported

^a Event = initiation of next anti-CLL treatment or death

^b Hazard ratio < 1 favours venetoclax

Figure 3: Kaplan-Meier plot of time to next anti-CLL treatment for CLL-14 (ITT; 23 August 2019)



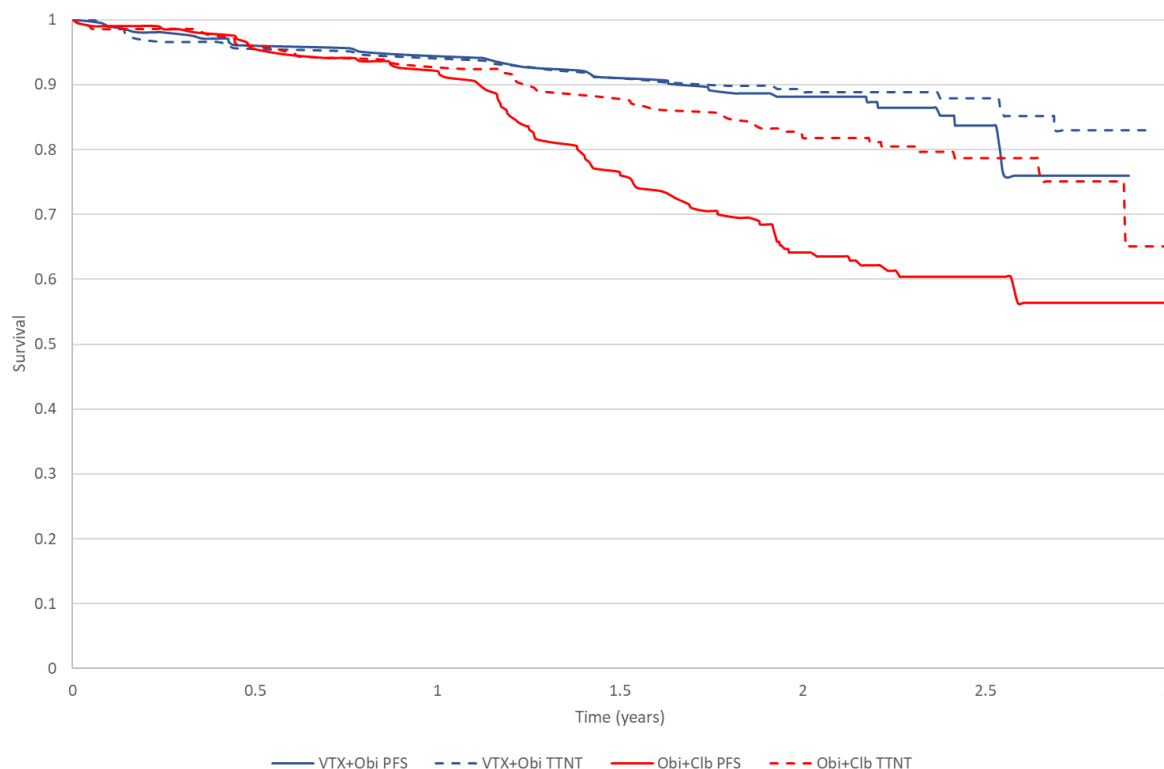
Source: Figure 3, p.3 of VTX_PBAC submission_updated data.docx

Abbreviations: CLL, chronic lymphocytic leukaemia; ITT, intention-to-treat; GC1b, chlorambucil + obinutuzumab; VEN+G, venetoclax + obinutuzumab

Note: Censored, criteria not defined

- 6.19 The risk of starting a new anti-CLL treatment was statistically significantly lower for patients treated with venetoclax + obinutuzumab compared to chlorambucil + obinutuzumab (stratified HR 0.60, 95% CI: 0.37, 0.97), based on a median follow up of 29.06 months. The median TTNT was not reached in either treatment arm.
- 6.20 TTNT was defined as the time from randomisation to initiation of a new anti-CLL treatment or death. Patients could initiate subsequent therapy before or after disease progression (three patients in each treatment arm received new treatments prior to disease progression). There was no criteria in the CLL-14 study protocol for the management of post-progression treatments. The PSCR stated that the absence of such protocols meant that patients were only initiated on subsequent therapy when it was clinically meaningful and clinically appropriate to do so.
- 6.21 Figure 4 shows superimposed Kaplan-Meier plots for PFS over TTNT from CLL-14.

Figure 4: Superimposed Kaplan-Meier plots for PFS over TTNT from CLL-14 (ITT; 17 August 2018)



Source: Kaplan Meier data included in PBAC_Section 3_CUA_VTX+Obi_Final spreadsheet provided with the submission

Abbreviations: Obi, obinutuzumab; Clb, chlorambucil; ITT, intention-to-treat; PFS, progression free survival; TTNT, time to next anti-CLL treatment; VTX, venetoclax

- 6.22 The ESC noted that differences between PFS and TTNT were not consistent between treatment arms. For patients treated with chlorambucil + obinutuzumab, the Kaplan Meier curves for PFS and TTNT diverged from end-of-treatment, while for patients treated with venetoclax + obinutuzumab, PFS and TTNT showed no divergence until the tail of survivors, where small patient numbers impacted the reliability of the data. The data suggest that larger proportions of patients treated with chlorambucil + obinutuzumab experienced delayed or no new anti-CLL treatment after disease progression, while patients treated with venetoclax + obinutuzumab experienced little or no delay.
- 6.23 Differences between treatment arms in time from disease progression to initiation of new anti-CLL treatments were not adequately explained in the submission. The PSCR stated that the post-progression treatment patterns between the treatment arms “could not be easily interpreted”. The ESC noted that in the economic model the utility decrement applied to the time in the progressed but well health state (i.e. the time between progression and retreatment) had an effect on the ICER, but agreed with the PSCR that the differences could not be easily explained. Overall the ESC considered TTNT was likely a more relevant indicator of treatment effect (compared to PFS) and

that in clinical practice TTNT following progression would be more similar to that seen in the chlorambucil + obinutuzumab arm.

- 6.24 Results for overall response (rate difference = 13.4%, 95% CI: 5.5, 21.4) and complete response to treatment (rate difference = 26.4%, 95% CI: 17.4, 35.7), duration of response (stratified HR = 0.31, 95% CI: 0.20, 0.50), MRD negativity (MRD assessed in the bone marrow odds ratio = 6.40, 95% CI: 4.10, 9.98) and MRD negativity in patients achieving complete response (CR/CRi; MRD assessed in the bone marrow odds ratio = 4.28, 95% CI: 2.56, 7.18), favoured venetoclax + obinutuzumab compared to chlorambucil + obinutuzumab.
- 6.25 In CLL-14, mean utilities, measured using the EQ-5D-3L were high at baseline and comparable between treatment arms (■■■■ for venetoclax + obinutuzumab and ■■■■ for chlorambucil + obinutuzumab). Mean utility scores remained stable throughout treatment and follow-up in both treatment arms.

Subgroup analyses

- 6.26 Pre-specified subgroup analyses conducted for investigator assessed PFS showed substantial variation in the estimated treatment effect across subgroups (particularly for IGVH mutational status, cytogenetic hierarchical type and Binet stage at screening). However, results should be interpreted with caution, given the small sample size/small numbers of events and wide confidence intervals for several subgroups. Analyses of treatment effect interaction between subgroups were not reported.
- 6.27 However, during the evaluation, an abstract was identified that presented results of subgroup analyses of genetic markers from Trial CLL-14 (Tausch 2019). It stated that there was a statistically significant treatment interaction for IGVH status ($p=0.03$), indicating an improved treatment effect for venetoclax + obinutuzumab compared with chlorambucil + obinutuzumab in patients with unmutated IGVH. Treatment effect interactions between other subgroups were not reported.
- 6.28 The PSCR stated that at the updated August 2019 data-cut, there was no evidence of treatment effect modification by IGHV mutation status. The risk of disease progression or death was reduced by 77% (unstratified HR = 0.23; 95% CI: 0.15, 0.35) in the unmutated IGHV subgroup and by 67% (unstratified HR = 0.33; 95% CI: 0.16, 0.70) in the mutated IGHV subgroup in the venetoclax + obinutuzumab arm of CLL-14 (test for subgroup differences, $p=0.40$). There were similar results for patients with TP35 mutation/del(17p). The ESC noted that the number of patients with TP35 mutation/del(17p) were small and therefore considered that any differences with respect to cytogenetic type would not be strong treatment effect modifiers.

Comparative harms

- 6.29 Table 7 summarises the proportions of patients reporting adverse events for the CLL-14 trial, and numbers of events reported in CLL-14. No updated CLL-14 safety data were provided.

Table 7: Summary of key adverse events in CLL-14 (safety population; 17 August 2018)

Adverse events n (%) [# events]	Venetoclax + obinutuzumab (N=212)	Chlorambucil + obinutuzumab (N=214)	RR (95% CI)	RD (95% CI)
Patients with ≥ 1 adverse event	200 (94.3%) [2,448 events]	213 (99.5%) [2,074 events]	0.95 (0.92, 0.98)	-0.5 (-0.08, -0.02)
Discontinuations due to adverse events	4 (1.9%)	1 (0.5%)	4.04 (0.46, 35.8)	0.01 (-0.01, 0.04)
Serious adverse events in >1 patient	104 (49.1%) [202 events]	90 (42.1%) [179 events]	1.17 (0.95, 1.44)	0.07 (-0.02, 0.16)
Grade 3 or 4 adverse events	167 (78.8%) [344 events]	164 (76.6%) [239 events]	1.03 (0.93, 1.14)	0.02 (-0.06, 0.10)
Adverse events resulting in death	16 (7.5%)	8 (3.7%)	2.02 (0.88, 4.62)	0.04 (-0.01, 0.08)
Deaths (due to any cause)	20 (9.3%)	16 (7.5%)	1.26 (0.67, 2.37)	0.02 (-0.03, 0.07)

Source: Table 41, p.80 of the submission; Table 48, p.163, Table 51, p.168, Table 62, p.185 of the CLL-14 Clinical Study Report, Attachment 4 to the submission; and Table 2 of the PSCR

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukaemia; RD, risk difference; RR, relative risk

- 6.30 In Trial CLL-14, a larger proportion of patients treated with chlorambucil + obinutuzumab reported at least one adverse event (AE) compared to patients treated with venetoclax + chlorambucil, however patients treated with venetoclax + obinutuzumab experienced more AEs compared with chlorambucil + obinutuzumab. Treatment with venetoclax + obinutuzumab was also associated with larger numbers of serious AEs and grade 3 or 4 AEs compared with chlorambucil + obinutuzumab, and venetoclax + obinutuzumab was associated with a larger proportion of AEs resulting in death.
- 6.31 The PSCR noted that the differences in serious AEs, grade 3 or 4 AEs and AEs resulting in death were not statistically significant. In addition, the PSCR stated that the rate of AEs resulting in death during the treatment period was comparable in both arms, with a higher rate of fatal AEs in the venetoclax + obinutuzumab arm post-treatment; however, that due to the long latency period from last dose of study drug and the potential for confounding, a causal association with venetoclax treatment and fatal AEs post-treatment was considered unlikely.
- 6.32 The ESC expressed concerns over the safety profile of venetoclax with respect to the higher point estimates for serious AEs and AEs resulting in death in the venetoclax + obinutuzumab arm of CLL-14. The ESC considered that the lack of a statistically significant difference may not be sufficient to establish non-inferiority, particularly in light of the high upper 95% confidence interval for adverse events resulting in death.
- 6.33 Table 8 summarises the treatment emergent AEs of interest and the most frequently reported serious AEs for the CLL-14 trial.

Table 8: Summary of treatment emergent adverse events of special interest and serious adverse events reported in CLL-14 (safety population; 17 August 2018)

Adverse events n (%) [# events]	Venetoclax + obinutuzumab (N=212)	Chlorambucil + obinutuzumab (N=214)	RR (95% CI)	RD (95% CI)
Treatment emergent adverse events of special interest reported by more than 1 patient				
Neutropenia Grade 3 or 4	119 (56.1%) [327 events]	112 (52.3%) [250 events]	1.07 (0.90, 1.28)	0.04 (-0.06, 0.13)
Thrombocytopenia Grade 3 or 4	32 (15.1%) [51 events]	33 (15.4%) [43 events]	0.98 (0.63, 1.53)	-0.00 (-0.07, 0.07)
Infections/infestations Grade ≥ 3	41 (19.3%) [58 events]	35 (16.4%) [51 events]	1.18 (0.79, 1.78)	0.03 (-0.04, 0.10)
Second primary malignancies	29 (13.7%) [35 events]	22 (10.3%) [29 events]	1.33 (0.79, 2.24)	0.03 (-0.03, 0.10)
Tumour lysis syndrome	3 (1.4%) [3 events]	5 (2.3%) [5 events]	0.61 (0.15, 2.50)	-0.01 (-0.04, 0.02)
Infusion related reactions Grade ≥ 3	25 (11.8%) [36 events]	23 (10.7%) [33 events]	1.10 (0.64, 1.87)	0.01 (-0.05, 0.07)
Serious adverse events reported by more than 1 patient (≥ 2% in any treatment arm)				
Febrile neutropenia	11 (5.2%)	8 (3.7%)	-	-
Pneumonia	10 (4.7%)	9 (4.2%)	-	-
Infusion-related reaction	9 (4.2%)	13 (6.1%)	-	-
Pyrexia	8 (3.8%)	7 (3.3%)	-	-
Sepsis	6 (2.8%)	2 (0.9%)	-	-
Thrombocytopenia	2 (0.9%)	5 (2.3%)	-	-
Atrial fibrillation	1 (0.5%)	3 (1.4%)	-	-
Acute coronary syndrome	0	0	-	-
Tumour lysis syndrome	1 (0.5%)	4 (1.9%)	-	-

Source: Table 41, p.80 of the submission; Table 68, p.199; Table 70, p.201, Table 71, p.203, Table 72, p.205, tables on pp.2122-2123 of CLL-14 CSR; Attachment 4 to the submission; and Table 2 of the PSCR

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukaemia; RD, risk difference; RR, relative risk

- 6.34 In Trial CLL-14, larger proportions of patients treated with venetoclax + obinutuzumab reported grade 3 or 4 neutropenia, grade 3 or higher infections/infestations and second primary malignancies, compared with patients treated with chlorambucil + obinutuzumab.
- 6.35 The ESC noted that although the rates of the AEs were not statistically significantly different, they were likely to be clinically meaningful. The point estimates were numerically higher for neutropenia, infections/infestations, second primary malignancies and infusion related reactions. The ESC considered that the lack of a statistically significant difference may not be sufficient to establish non-inferiority, particularly in light of the high upper 95% confidence intervals.
- 6.36 The pre-PBAC response noted that, although the incidence of fatal AEs was numerically higher in the venetoclax + obinutuzumab arm of CLL-14, the rate of fatal AEs during the treatment period (12 months) was comparable between arms (2.3% vs 1.9%, respectively), with a higher rate observed post-treatment in the venetoclax + obinutuzumab arm (5.1% vs. 1.9%). Of the 11 fatal AEs occurring post-treatment in the venetoclax + obinutuzumab arm, only one was assigned by the Investigator as treatment related.

Benefits/harms

- 6.37 On the basis of direct comparison evidence presented in the submission, for every 100 patients treated for 12 months with venetoclax + obinutuzumab in comparison with chlorambucil + obinutuzumab:
- Approximately 3 additional patients will remain progression free at one year, approximately 24 additional patients will remain progression free at two years, and approximately 32 additional patients will remain progression free at three years.
 - Approximately 1 additional patient will not have initiated the next line of treatment at one year, approximately 8 additional patients will not have initiated the next line of treatment at two years and approximately 12 additional patients will not have initiated the next line of treatment at three years.
 - Approximately 4 additional patients may experience an AE resulting in death after a median follow-up of 29 months.
 - Approximately 4 additional patients may experience life threatening or severe neutropenia after a median follow-up of 29 months.
 - Approximately 3 additional patients may experience life threatening or severe infection or infestation after a median follow-up of 29 months.
 - Approximately 3 additional patients may experience a second primary malignancy after a median follow-up of 29 months.

Clinical claim

- 6.38 Based on the direct comparison of venetoclax + obinutuzumab versus chlorambucil + obinutuzumab, in previously untreated CLL patients with coexisting conditions, the submission described venetoclax + obinutuzumab as superior in terms of effectiveness and non-inferior in terms of safety compared to chlorambucil + obinutuzumab.
- 6.39 The ESC considered this claim was supported in terms of effectiveness by statistically significant outcomes in PFS and TTNT, in addition to results for complete response and MRD negativity. However, the following issues should be considered:
- While venetoclax + obinutuzumab demonstrated an improvement in PFS compared with chlorambucil + obinutuzumab, the clinical importance of this difference was unclear given the lack of clinically important OS data. Further, many patients treated with chlorambucil + obinutuzumab do not appear to require treatment immediately following progression (i.e. progressed but well) and patient reported outcomes did not suggest any substantial decrements to quality of life associated with progression. The pre-PBAC response claimed that PFS has been shown to be a surrogate for OS with other anti-CLL agents. The PBAC noted this was supported by the clinician during the sponsor hearing.
 - The robustness of reported TTNT results is uncertain given the lack of protocols for initiating subsequent therapy and the potential for bias due to the open label

nature of the trial. Overall, there appeared to be different post-progression treatment patterns between treatment arms, which could not be easily explained.

- 6.40 Overall, the PBAC accepted the claim of superior clinical effectiveness.
- 6.41 The ESC considered that the claim of non-inferior safety was uncertain as:
- Venetoclax + obinutuzumab was associated with higher point estimates for serious and grade 3/4 AE rates (primarily neutropenia, infections/infestations and secondary primary malignancies), compared to chlorambucil + obinutuzumab. Venetoclax + obinutuzumab was also associated with a higher point incidence of deaths due to AEs compared with chlorambucil + obinutuzumab. The PSCR argued that there were no statistically significant differences in the proportion of subjects experiencing key safety events. The ESC considered that the lack of a statistically significant difference was not sufficient to establish non-inferiority, particularly in light of the high upper 95% confidence intervals, and that the differences were likely to be clinically meaningful.
- 6.42 Overall, the PBAC considered it was uncertain whether venetoclax + obinutuzumab was non-inferior to chlorambucil + obinutuzumab. The impact of higher AEs could be further explored in the economic evaluation.

Economic analysis

- 6.43 The submission presented a cost-effectiveness analysis comparing venetoclax + obinutuzumab with chlorambucil + obinutuzumab.
- 6.44 The submission presented a stepped economic evaluation of venetoclax + obinutuzumab compared to chlorambucil + obinutuzumab as first-line treatment for CLL patients with coexisting conditions who are inappropriate for fludarabine based chemo-immunotherapy, based on extrapolated differences in PFS and TTNT curves from the CLL-14 trial and other modelled variables. The economic evaluation was presented as a cost-effectiveness/cost-utility analysis.

Table 9: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	venetoclax + obinutuzumab, chlorambucil + obinutuzumab
Time horizon	10 years in the model base case versus mean duration of follow-up of 29.06 months in the trial
Outcomes	Progression free life years; life years free from relapsed/refractory disease; quality adjusted life years
Methods used to generate results	Partitioned survival analysis
Health states	First-line progression free, first-line progressed disease, relapsed/refractory disease, dead
Cycle length	1 month
Transition probabilities	Extrapolated OS, PFS and TTNT (includes death events) survival curves based on data from the CLL-14 trial
Extrapolation method ^a	OS was assumed to be the same between treatment arms. Modelled OS was based on the chlorambucil + obinutuzumab arm, extrapolated using an exponential function with adjustments to ensure that OS did not exceed general population survival. PFS was independently extrapolated for each treatment arm using exponential functions. A two-phase extrapolation was used for the chlorambucil + obinutuzumab arm to account for differences in PFS while

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Component	Summary
	<p>on and off treatment. The same hazards were assumed for both treatment arms based on chlorambucil + obinutuzumab after 5 years (risk convergence).</p> <p>TTNT survival was independently extrapolated for each treatment arm using exponential functions. A two-phase extrapolation was used for the chlorambucil + obinutuzumab arm to account for differences in TTNT survival while on and off treatment. The same hazards were assumed for both treatment arms based on chlorambucil + obinutuzumab after 5 years (risk convergence). The ESC, noting that TTNT was associated with a utility decrement and cost in the model, had concerns with the reliability of this measure, given that the differences between the treatment arms in time from disease progression to initiation of new anti-CLL treatments could not be explained.</p> <p>The ESC noted that 89% of incremental progression-free life years, 93% of incremental life years free of relapsed/refractory disease, 91% of incremental QALYs and -251% of incremental costs are accrued in the extrapolated period.</p>
Health related quality of life	<p>Despite trial data being available, utility values were derived from published sources (Kosmas 2015) with additional assumptions. The ESC considered that applying Kosmas 2015 utility weights overestimated the utility decrements versus the CLL-14 trial for patients on treatment (IV and oral).</p>
Health resource use and costs	<p>First line drug and administration costs were based on drug exposure reported in the CLL-14 trial with costings based on PBS prices^a (venetoclax + obinutuzumab: \$ ██████, chlorambucil + obinutuzumab: \$41,996).</p> <p>Relapsed/refractory drug costs were estimated from a post hoc analysis of the time to initiation of subsequent treatment censoring death events) in the CLL-14 trial with costings for based on the post-PBAC cost minimisation analysis for the November 2018 venetoclax submission (ibrutinib monotherapy: \$ ██████).</p> <p>Health state costs were derived using health resource use from a published source (Paquete 2017), with mapping to Australian cost items. Costs for first line progression free and progressed disease were \$ ██████ per monthly cycle; relapsed/refractory health state costs were \$ ██████ per cycle. The ESC considered that Paquete 2017 significantly overestimated these costs.</p>

Source: Table 47, p97 of the submission

IV = intravenous; OS = overall survival; PFS = progression free survival; TTNT = time to next treatment

Note: The estimates presented in the submission were based on the published price of obinutuzumab as the sponsor was unaware of the effective price

^a Risk convergence is applied as an adjustment to the venetoclax + obinutuzumab progression free survival, time to next treatment and time to initiation of subsequent treatment curves, applying survival based on the hazards in the chlorambucil + obinutuzumab arm after a predetermined duration. Curve convergence is applied as an adjustment to the venetoclax + obinutuzumab progression free survival, time to next treatment and time to initiation of subsequent treatment curves by forcing convergence equivalent to the chlorambucil + obinutuzumab curves between two predetermined time points.

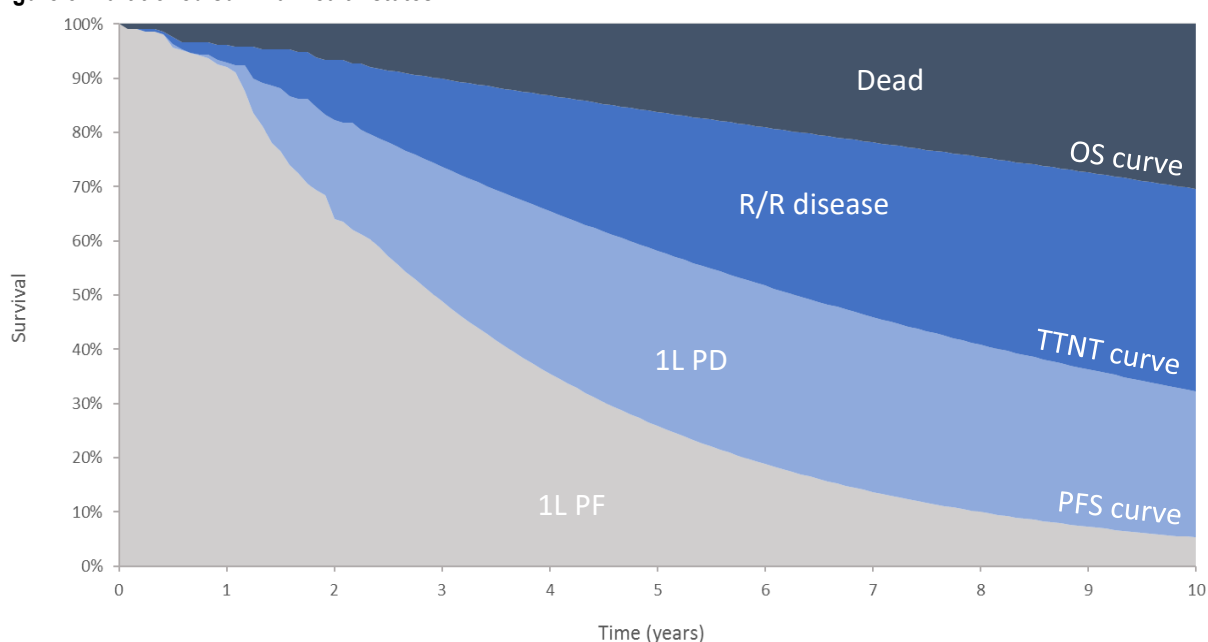
6.45 The submission stated that a 10-year time horizon has previously been considered appropriate by the PBAC for older, previously untreated CLL patients with multiple comorbidities (paragraph 7.17, Obinutuzumab Public Summary Document, July 2014 PBAC meeting). A 10-year time horizon may not be sufficient to capture the costs and consequences of the introduction of venetoclax + obinutuzumab on the management of previously untreated CLL patients. However, given the limited follow-up of Trial CLL-14 (estimates included in the model based on 29 months), the ESC considered that extrapolation over a longer period would be subject to considerable uncertainty. The PBAC considered a 10 year time horizon appropriate.

6.46 A partitioned survival analysis design was implemented to distribute patients between model health states. The PFS, TTNT and OS curves, derived from Trial CLL-14, were used to distribute patients between the model health states:

- The area below the PFS curve relates to patients in the first-line progression free health state;
- The area between the PFS and TTNT curves relates to patients in the first-line progressed disease (progressed but well) health state;
- The area between the TTNT and OS curves relates to patients in the relapsed/refractory disease health state; and
- The area above the OS curve relates to patients in the dead state.

6.47 The relationship between survival curves and health states in the economic model is illustrated in the figure below.

Figure 5: Partitioned survival health states



Source: Figure 29, p108 of the submission

Abbreviations: 1L PD, first-line progressed disease; 1L PF, first-line progression free; OS, overall survival; PFS, progression free survival; R/R, relapsed/refractory; TTNT, time to next treatment.

6.48 The ESC were concerned about the inconsistencies between the PFS and TTNT curves which were incorporated into the model, as the difference in time from disease progression to initiation of new anti-CLL treatments between treatment arms could not be explained. A number of patients from the chlorambucil + obinutuzumab arm did not require treatment immediately following progression, instead entering the 'progressed but well' health state. The ESC noted that time in the 'progressed but well' health state was associated with an assumed utility decrement and costs.

6.49 Health state utility values used in the economic model are summarised in the table below.

Table 10: Health state utility values

Health state	Value	Source
First line progression free		
- On IV treatment (cycles 1-6)	0.67	Based on utility values reported for PFS on initial therapy, IV treatment in the Kosmas 2015 publication. This contrasts with a mean utility score of 0.83-0.86 in Cycles 1-6 of the CLL-14 trial when patients received combination therapy with IV obinutuzumab
- On oral treatment (cycles 7-12)	0.71	Based on utility values reported for PFS on initial therapy, oral treatment in the Kosmas 2015 publication. This contrasts with a mean utility score of 0.83-0.86 in Cycles 7-12 of the CLL-14 trial when patients received single agent oral therapy
- Off treatment	0.82	Based on utility values reported for PFS after receiving an initial course of treatment in the Kosmas 2015 publication.
First line progressive disease "progressed but well"	0.74	Assumption. Based on midpoint between the off-treatment progression free utility (0.82) and the untreated progression after first line treatment utility (0.66)
Relapsed/refractory disease	0.66	Based on utility valued reported for CLL progressing following receiving first line treatment and not currently receiving any therapy in the Kosmas 2015 publication

Source: Table 80, p.143 of the submission

Abbreviations: CLL, chronic lymphocytic leukaemia; IV, intravenous; PFS, progression-free survival

6.50 The ESC noted that within trial quality of life data were collected in CLL-14 for the 12 month period following initial treatment and prior to subsequent treatment (see Table 11 and Figure 6). The ESC considered that the on treatment utility values applied in the model from Kosmas were low (0.67 and 0.71) compared to the mean utility scores of █████ to █████ observed in both treatment arms of CLL-14, which suggested that treatment exposure was not associated with a utility loss. The ESC considered that the utilities applied in the model were underestimated, i.e. the numbers overestimated the decrement to quality of life.

6.51 Acknowledging that the Kosmas data were generated using the time-trade off method and the trial quality of life data were generated using the EQ-5D, the ESC noted that the PBAC Guidelines (version 5.0, 2016) indicate a preference for trial based utility data when available, unless there are significant concerns about the reliability or relevance of the trial-based utilities. The submission claimed that the trial-based utility estimates were not used as they only reflected PFS and did not capture the utility loss associated with progression or subsequent therapy. However, the ESC considered the use of the Kosmas utilities in the base case was not adequately justified as, to capture post progression utility values, CLL-14 assessed patients at the time of the subsequent treatment visit, but before any procedures or drug infusions had been performed.

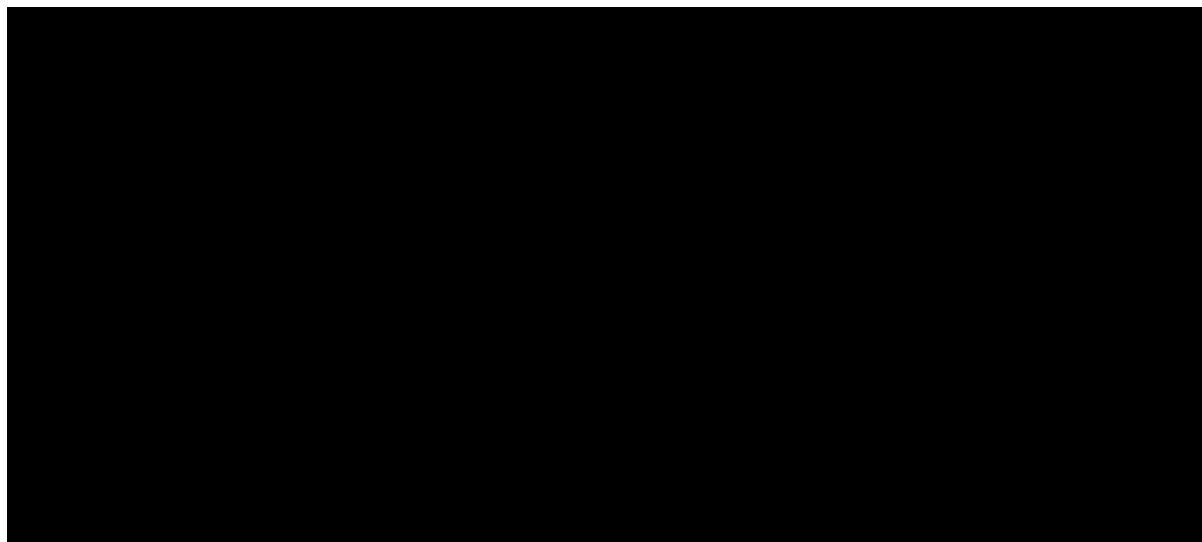
Table 11: Baseline quality of life of patients in CLL-14: EQ-5D

Parameter	Venetoclax + obinutuzumab	Obinutuzumab + chlorambucil
N	██████████	██████████
Mean (SD)	██████████ (██████████)	██████████ (██████████)
Median [IQR]	██████████ [██████████-██████████]	██████████ [██████████-██████████]
Range (min – max)	██████████ - ██████████	██████████ - ██████████

Source: Table 75, p.138 of the submission

Abbreviations: IQR, interquartile range; SD, standard deviation; EQ-5D, EuroQol 5 dimension questionnaire

Figure 6: Change from baseline EQ-5D utility value in CLL-14 ITT population



Source: Figure 61, p.139 of the submission

6.52 The PBAC noted that utility values from the Kosmos (2015) were used when obinutuzumab was considered in March 2015. In addition, the PBAC noted that it had previously accepted a lower utility value for patients who were in the ‘asymptomatic progression’ health state. However, the PBAC noted the trial-based utilities in CLL-14 were inconsistent with the Kosmos utilities. The PBAC also noted that the CLL treatment landscape had changed significantly since the recommendation of obinutuzumab + chlorambucil in the first-line setting, with numerous efficacious treatments now available in the relapsed or refractory setting.

6.53 Key drivers of the economic model are summarised in the table below.

Table 12: Key drivers of the model

Description	Method/Value	Impact
Duration of treatment effect	<p>OS, PFS and TTNT survival curves were extrapolated from 2.33 years in the CLL-14 trial to 10 years in the economic model based on exponential survival functions. Risk convergence between treatment arms was assumed to occur after 5 years. The PSCR stated that the model was conservative as these curves were extrapolated for only 20 months (i.e. from 2.33 to five years), after which no treatment effect was assumed. The ESC considered that curve convergence from 5 years rather than risk convergence would be more conservative and a more informative base case.</p> <p>The risk convergence time point (5 years) was based on an arbitrary assumption. The ESC considered there are insufficient clinical data available to reliably estimate the duration of effect for venetoclax + obinutuzumab.</p>	High, direction unclear

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Description	Method/Value	Impact
Utility values	<p>Utilities were based on a published study (Kosmas 2015), which reported time trade-off valuation of CLL health state vignettes by a UK general population sample (100 individuals; conducted in 2014 or earlier).</p> <p>The applicability of the Kosmas 2015 study was uncertain as the health state vignettes were not included in the publication. In particular, it was unclear whether the health state vignettes were representative of the current clinical management of CLL patients given the substantial changes in available treatment options over time.</p> <p>Utility values derived from the Kosmas 2015 publication did not appear consistent with the reported utility values from the CLL-14 trial. The trial data suggest that treatment exposure was not associated with a substantial utility loss. The ESC considered that the utilities used in the on treatment period overestimated the decrement to quality of life.</p>	High, favours venetoclax
Relapsed/refractory drug costs	<p>Proportions of patients eligible for relapsed/refractory treatment were based on an exponential extrapolation of TTNT data from Trial CLL-14, censored for death (post hoc analysis), applied to the proportions of patients in the PFS and first line progressed disease states. Unit cost of relapsed/refractory treatment were based on the cost of ibrutinib included in the post-PBAC cost-minimisation analysis for the November 2018 venetoclax submission.</p> <p>The assumption that all patients receive ibrutinib monotherapy as second-line treatment was inconsistent with expert advice that indicated that the choice of subsequent therapy will depend on the first-line treatment regimen as well as the duration of progression free survival and resulted in substantial cost-offsets over the extrapolated time period. The economic evaluation only considered second-line treatment costs, while in clinical practice patients may receive multiple lines of therapy.</p>	High, direction unclear
Health state costs	<p>Resource use in progression free and relapsed/refractory disease were based on resource use from Paquete 2017 (derived from a panel of Portuguese experts in 2014), mapped to Australian PBS, MBS and hospitalisation items.</p> <p>The ESC considered the applicability of health resource use from Portugal in 2014 to current clinical practice was unclear given potential differences in healthcare systems and rapidly changing treatment pathways for CLL patients.</p> <p>The submission poorly justified the mapping of health resource items to Australian costs, with substantial issues regarding ambiguous descriptions, additional assumptions and coding errors.</p> <p>The ESC noted that the health state costs estimated in the submission were 2-5 times higher than other published estimates and were approximately 4 times higher than previously estimated for relapsed/refractory disease in the March 2017 venetoclax submission. As proposed by the evaluation's alternative base case, the PSCR agreed to halving these costs.</p>	High, favours venetoclax

Source: Constructed during the evaluation

Abbreviations: OS, overall survival; PFS, progression-free survival; TTNT, time to next treatment survival

6.54 The submission claimed that venetoclax + obinutuzumab is non-inferior in terms of safety compared to chlorambucil + obinutuzumab and therefore excluded the costs of adverse events from the base case analysis. The evaluation considered that this was

not appropriate given the higher event rates for serious and grade 3/4 adverse events in CLL-14 and the concerns regarding the claim of non-inferior safety. The PSCR argued that adverse event costs should not be included due to the differences not being statistically significant (despite being numerically higher). The ESC considered it was inappropriate to include differential health state and treatment specific utilities despite no (numerical) differences, whilst excluding costs for numerically higher adverse events.

6.55 Although a detailed costing of tumour lysis syndrome (TLS) was reported as an Attachment to the submission, the economic evaluation did not include the costs associated with the prophylactic management of TLS with venetoclax. The evaluation considered that this was inappropriate as TLS prophylaxis is associated with substantial hospitalisation costs and the costs were included in the cost-minimisation analysis considered by the PBAC in November 2018 between venetoclax + rituximab and ibrutinib for the treatment of relapsed or refractory CLL. The PSCR agreed to the inclusion of these costs.

6.56 The results of the modelled economic evaluation, based on published prices, are summarised below.

Table 13: Stepped economic evaluation of venetoclax + obinutuzumab compared with chlorambucil + obinutuzumab

Type of resource item	Venetoclax + obinutuzumab	Chlorambucil + obinutuzumab	Increment
Step 1a: Outcome progression free survival, based on mean trial follow-up of 29 months; first-line drug and administration costs only			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Progression free life years	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per progression free life year gained			\$ [REDACTED]
Step 1b: Outcome time to next treatment, based on mean trial follow-up of 29 months; first-line drug and administration costs only			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Time to next treatment (years)	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per additional year free from relapsed/refractory disease			\$ [REDACTED]
Step 2: Outcome QALYs (utilities applied to health states), based on mean trial follow-up of 29 months; first-line drug and administration costs only			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]
Step 3: Outcome QALYs, based on mean trial follow-up of 29 months; health state costs and relapsed/refractory disease treatment costs included with first-line drug and administration costs			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]
Step 4: Extrapolated costs and outcomes to 10 years; outcome QALYs; first- and subsequent-line drug and administration costs and health state costs included			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]

Source: Table 107, p162 of the submission and PBAC_Section 3_CUA_VTX+Obi_final spreadsheet provided with the submission
Abbreviations: QALY, quality adjusted life year

- 6.57 The difference in incremental cost between treatment arms was primarily driven by the cost of the venetoclax component, with cost offsets associated with relapsed/refractory treatment and health state costs. The difference in health outcomes was primarily driven by the additional time spent in the progression free health state (associated with better quality of life) for patients treated with venetoclax + obinutuzumab, compared with chlorambucil + obinutuzumab. The extrapolation of treatment benefits beyond the clinical trial data had the largest impact on the stepped economic evaluation (i.e. from Step 3 to 4).
- 6.58 Based on the economic model presented in the submission, treatment with venetoclax + obinutuzumab was associated with a cost per QALY gained of \$15,000 - \$45,000 compared to chlorambucil + obinutuzumab for the treatment of first-line CLL patients with coexisting conditions who are inappropriate for fludarabine based chemo-immunotherapy. The ESC considered that the cost-effectiveness estimate should not be considered reliable given the unknown duration of effect associated with venetoclax + obinutuzumab treatment versus chlorambucil + obinutuzumab, the inconsistency between modelled and reported utility values and the magnitude of health state costs compared to other sources.
- 6.59 The results of sensitivity analyses indicate that the model is most sensitive to time horizon, the utility associated with first-line disease progression (progressed but well) and relapsed/refractory disease, health state costs, the costs of relapsed/refractory treatment and the onset of convergence between treatment arms.
- 6.60 The ESC noted that the submission explored the use of two forms of convergence: risk convergence and curve convergence. Risk convergence was applied as an adjustment to the venetoclax + obinutuzumab progression free survival, time to next treatment and time to initiation of subsequent treatment curves, by applying survival based on the hazards in the chlorambucil + obinutuzumab arm after a predetermined duration (base case: HR = 1 from 5 years). Curve convergence was applied as an adjustment to the venetoclax + obinutuzumab progression free survival, time to next treatment and time to initiation of subsequent treatment curves by forcing convergence equivalent to the chlorambucil + obinutuzumab curves between two predetermined time points (base case: no curve convergence).

Table 14: Results of key sensitivity analyses

Analysis	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
Base case	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Time horizon (base case 10 years)			
5 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
8 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
15 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Health state utilities (base case: 1L PF=0.82; 1L PD=0.74; R/R 0.66)			
No utility loss until R/R treatment (1L PF=0.82, 1L PD=0.82, R/R 0.66)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Increased utility loss for 1L PD (1L PF=0.82, 1L PD=0.66, R/R 0.66)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
No utility loss until R/R treatment; halve disutility of R/R (1L PF=0.82, 1L PD=0.82, R/R=0.74)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Health state costs (base case: 1L PF=\$218.76; 1L PD=\$218.76; R/R=\$1,141.78)			
Health state costs × 0.5	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
1L PD costs half-way between 1L PF and R/R costs (\$680.27)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Remove health state costs	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Treatment costs for relapsed/refractory disease (base case \$ [REDACTED])			
× 1.5	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
× 0.5	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Risk convergence (base case venetoclax + obinutuzumab PFS and TTNT curves adjusted by applying a HR=1 relative to chlorambucil + obinutuzumab from 5 years)			
Risk convergence from 2.33 years (mean follow-up of Trial CLL-14)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Risk convergence from 4 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Risk convergence from 6 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Risk convergence from 8 years	\$ [REDACTED]	[REDACTED]	Dominant
Curve convergence (base case no curve convergence)			
Curve convergence between 2.33 years and 10 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Curve convergence between 4 and 10 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Curve convergence between 6 and 10 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Curve convergence between 8 and 10 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Curve convergence between 2.33 and 8 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Curve convergence between 4 and 8 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Curve convergence between 6 and 8 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Curve convergence between 2.33 and 5 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Curve convergence between 3 and 5 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]

Source: Table 112, p165 of the submission and additional analyses conducted during the evaluation using PBAC_Section 3_CUA_VTX+Obi_Final spreadsheet provided with the submission

Abbreviations: 1L PD, first-line progressed disease; 1L PF, first-line progression free; PFS, progression free survival; QALY, quality adjusted life year; R/R, relapsed refractory; TTNT, time to next treatment

*Disutility of IV treatment applied in both treatment arms for 6 months of treatment with obinutuzumab; disutility of oral treatment applied in both treatment arms for the following 6 months of treatment with venetoclax or chlorambucil alone.

6.61 Multivariate sensitivity analyses were conducted during the evaluation using an alternative base case, which includes the costs of TLS prophylactic management (\$ [REDACTED], based on costs presented in the November 2018 venetoclax submission), the costs of serious adverse events (\$ [REDACTED]/patient in the venetoclax + obinutuzumab arm and \$ [REDACTED]/patient in the chlorambucil + obinutuzumab arm), assuming no utility loss

due to treatment exposure or first-line progression (i.e. ‘on treatment’ and ‘progressed but well’ utility = 0.82), and halving health state costs. The ESC noted that the evaluator proposed alternative base case did not address the issue of a reasonable duration of treatment effect or alter risk and curve convergence.

Table 15: Results of multivariate sensitivity analyses conducted during the evaluation

Analysis	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
Alternative base case (no utility loss due to treatment exposure or first-line progression; halve health state costs; include costs of adverse events; include TLS prophylactic management based on November 2018 venetoclax submission)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Disutility associated with R/R disease (base case utility 0.66)			
25% reduction in disutility (utility 0.70)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
50% reduction in disutility (utility 0.74)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
75% reduction in disutility (utility 0.78)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Treatment costs for relapsed/refractory disease (base case \$ [REDACTED])			
×1.5	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
×0.5	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Risk convergence (base case venetoclax + obinutuzumab PFS and TTNT curves adjusted by applying survival based on a HR=1 relative to chlorambucil + obinutuzumab from 5 years)			
Risk convergence from 2.33 years (mean follow-up of Trial CLL-14)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Risk convergence from 4 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Risk convergence from 6 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Risk convergence from 8 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Curve convergence (base case no curve convergence)			
Curve convergence between 2.33 years and 10 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Curve convergence between 4 and 10 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Curve convergence between 5 and 10 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Curve convergence between 6 and 10 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Curve convergence between 8 and 10 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]

Source: Sensitivity analyses conducted during the evaluation using PBAC_Section 3_CUA_VTX+Obi_Final spreadsheet provided with the submission

Abbreviations: QALY, quality adjusted life year; R/R, relapsed refractory; TTNT, time to next treatment

- 6.62 Based on the multivariate analyses conducted during the evaluation, correcting for favourable assumptions included in the model base case resulted in ICERs exceeding \$75,000 – \$105,000 per QALY gained. Venetoclax + obinutuzumab is unlikely to be cost-effective against chlorambucil + obinutuzumab without a further price reduction.
- 6.63 The PSCR presented the results of a respecified base case, which was based on two of the four changes that were included in the evaluator proposed alternative base case (halving health state costs; including TLS prophylaxis costs). The PSCR did not accept the changes to the utility values or the inclusion of serious adverse event costs. The PSCR presented an ICER of \$45,000 - \$75,000 per QALY for the respecified base case.
- 6.64 The ESC considered that the respecified base case should be based on the evaluation corrected assumptions which incorporate the trial-based utility data for the pre-progression and post-progression health states and include serious adverse event

costs, halve the health state costs and include costs related to TLS prophylaxis. The ESC also advised that the respecified base case should include curve convergence from five years. This would result in an ICER of \$105,000 - \$200,000.

- 6.65 The pre-PBAC response argued that, while curve convergence may be more conservative, it is not plausible as it implies a reversal of relative treatment effect between years five and ten. By applying curve convergence from year five, it implies constant hazard ratios over this period, meaning that patients on venetoclax + are attributed approximately a 50% greater risk of TTNT and PFS events relative to patients on chlorambucil + obinutuzumab.
- 6.66 The pre-PBAC response presented the results of a respecified base case, which resulted in an ICER of \$45,000 - \$75,000 per QALY (August 2018 data-cut), and was based on:
- Utility data from Kosmos (2015). No utility loss was included due to treatment exposure (i.e. all patients in the progression free health state had a utility of 0.82); however, patients continued to receive a 0.08 utility loss in the progressed but well health state;
 - Inclusion of serious AE costs;
 - Halving the health state costs;
 - Inclusion of costs related to TLS prophylaxis; and
 - Risk convergence (rather than curve convergence) from year five.

Drug cost/patient

- 6.67 Drug costs per patient for venetoclax + obinutuzumab versus chlorambucil + obinutuzumab were estimated based on circumstances of use in the CLL-14 trial (12 months treatment duration), the proposed effective price for venetoclax and published prices for obinutuzumab and chlorambucil (see Table below). This approach to estimating the cost was consistent across the economic analysis and financial estimates.

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Table 16: Drug cost per patient per course for venetoclax + obinutuzumab versus chlorambucil + obinutuzumab

	Venetoclax + obinutuzumab		Chlorambucil + obinutuzumab	
	Venetoclax	Obinutuzumab	Chlorambucil	Obinutuzumab
Mean cumulative dose	-	7,355 mg ^a	757 mg ^b	7,464 mg ^b
Mean treatment duration	288.1 days ^c	-	-	-
Treatment days	Initial: 28 ^d Continuing: 260.1 ^e	-	-	-
Number of scripts per course	Initial: 1 Continuing: 8.7 ^f	7.355 ^g	3.784 ^h	7.464 ⁱ
Cost/script	Initial: \$ [REDACTED] (effective DPMQ) Continuing: \$ [REDACTED] (effective DPMQ)	\$5,459 (weighted published DPMA) ^j	\$133.63 (published DPMQ)	\$5,459 (weighted published DPMA) ^j
Cost/patient/course ^k	\$ [REDACTED]	\$40,149	\$506	\$40,748
Total cost/patient/course	\$ [REDACTED]		\$41,254	

Source: Table 64, p 113; Table 65, p 114; Table 86, p 145; Table 89, p 146 of the submission

^a Mean cumulative dose reported in the venetoclax + obinutuzumab arm of the CLL-14 trial

^b Mean cumulative dose reported in the chlorambucil + obinutuzumab arm of the CLL-14 trial

^c Mean treatment duration reported in the venetoclax + obinutuzumab arm of the CLL-14 trial

^d Assumption

^e Mean duration – initial script duration

^f 260.1 days x 400 mg (recommended dose per day) / 12,000 mg (dose per script)

^g Mean cumulative dose / 1000 mg (recommended dose per administration)

^h Mean cumulative dose based on 12 month course / 200 mg (dose per script)

ⁱ Mean cumulative dose / 1000 mg (recommended dose per administration)

^j Published DPMA for public hospitals (\$5,378.06) x use in public hospitals (0.29) + published DPMA for private hospitals (\$5,491.92) x use in private hospitals (0.71)

^k Scripts per course x cost/script

Estimated PBS usage & financial implications

6.68 This submission was not considered by DUSC. The submission used a mixed epidemiological/market share approach to estimate the utilisation and financial impact of venetoclax + obinutuzumab.

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Table 17: Key inputs and methods of derivation for financial estimates

	Value	Year 6 ^a	Source and comment
Incident CLL population	0.0067% of Australian population	■	2015 estimates from Australian Cancer Incidence and Mortality (AIHW 2018). Fixed incidence rate (ABS 2017). Assumption of no growth inconsistent with AIHW data suggesting increasing trend
Patients initiating first line therapy in year of diagnosis	■% of incident population	■	Expert panel survey (8 haematologist) suggesting ■% of CLL patients will receive treatment (CLL advisory board, May 2019 report). Assumed ■% uptake in the year of diagnosis and 30% over subsequent 4 years. Uptake rates may not be reliable due to the small sample of clinicians and wide range of responses (■% to ■%). Prevalent pool of untreated patients undergoing 'watch and wait' based on annual survival probabilities from 2007-2011 AIHW CLL mortality data applied to incident populations in each year. Prevalent pool inappropriately included treated and untreated patients in year of diagnosis
Patients from 'watch and wait' pool initiating first line therapy in subsequent years	■% per year over 4 years	■	Assumed linear uptake of ■% over 4 years (■% per year). Uptake rate assumed highly uncertain
Eligible patients	■%	■	Assumption based on expert panel survey estimates of patients physically unfit for chemo-immunotherapy, and additional patients likely to have cytogenetic aberrations/mutations. Assumption is uncertain; size of this population in clinical practice is unclear
Patients treated with venetoclax + obinutuzumab	Year 1: ■% Year 2-6: ■%	■	Assumed. Uncertain
Patients substituting from chlorambucil + obinutuzumab	100%	■	Assumed based on expert panel survey and comparison of market shares with and without the availability of venetoclax + obinutuzumab. Survey responses suggest availability of venetoclax + obinutuzumab will affect fitness assessments, and may increase the number of patients receiving 1 st line therapy. Comparison of market shares was uncertain due to potential market growth
Net change in patients initiating R/R therapy	Variable estimate	-■	Based on time to initiation of subsequent therapy (post-hoc analysis of CLL-14 trial data)
Net change in patients initiating ibrutinib monotherapy	<u>Treated with venetoclax + obinutuzumab</u> Yr 1-2: ■% ibrutinib Yr 3-6: ■% ibrutinib, 50% venetoclax + rituximab	-■	Estimated the total size of R/R market based on total scripts of ibrutinib each month from March 2019 to August 2019 (1000-1200 patients). Assumed a ■:■ split in market share between ibrutinib monotherapy and venetoclax + rituximab in all patients previously treated with chlorambucil + obinutuzumab. Assumption that ibrutinib monotherapy represents total relapsed/refractory market was inadequately justified, given use of venetoclax + rituximab is relatively immature and likely to continue growing. Assumed patients treated with venetoclax + obinutuzumab who relapse within 2 years can only receive ibrutinib monotherapy as subsequent therapy. Assumed after 2 years a ■:■ split between ibrutinib monotherapy and venetoclax + rituximab. Assumed use of venetoclax + obinutuzumab in first line setting will reduce the use of venetoclax + rituximab in R/R setting and increase use of ibrutinib monotherapy.
Net change in patients initiating venetoclax + rituximab	<u>Treated with chlorambucil + obinutuzumab</u> ■% ibrutinib, ■% venetoclax + rituximab	-■	The use of relapsed/refractory therapies in the budget impact analysis was inconsistent with the approach used in the economic model (assumed all relapsed/refractory patients receive ibrutinib monotherapy)

Source: Table 120, p.175 and the 'PBAC_Section 4_BIM_VTX+Obi_Final' Excel workbook of the submission

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Abbreviations: ABS, Australian Bureau of Statistics; CLL, chronic lymphocytic leukaemia; R/R, relapsed/refractory

^a Value estimated at each step in Year 6 of the financial estimates.

6.69 The submission presented the estimated use and cost of venetoclax (proposed effective price) + obinutuzumab (published price) for previously untreated CLL patients. Cost offsets were based on chlorambucil (published price) + obinutuzumab (published price), ibrutinib (effective price) and venetoclax (effective price) + rituximab (published price).

Table 18: Estimated use and financial implications

	Year 1 (2020)	Year 2 (2021)	Year 3 (2022)	Year 4 (2023)	Year 5 (2024)	Year 6 (2025)
Incident CLL patients						
Australian population	25,873,480	26,301,274	26,727,025	27,147,199	27,562,195	27,970,435
Incidence of CLL (0.0067%)	1,734	1,762	1,791	1,819	1,847	1,874
Patients commencing first line treatment						
During year of diagnosis (█%)	█	█	█	█	█	█
1-4 years after diagnosis, from 'watch & wait' pool (█% per year) ^a	█	█	█	█	█	█
Total first line patients	█	█	█	█	█	█
Estimated use of venetoclax + obinutuzumab						
Patients with coexisting conditions, unsuitable for fludarabine based chemo-immunotherapy (█%)	█	█	█	█	█	█
Uptake rates	█%	█%	█%	█%	█%	█%
Total patients	█	█	█	█	█	█
Venetoclax initial scripts (1 per course)	█	█	█	█	█	█
Venetoclax continuing scripts (8.7 per course)	█	█	█	█	█	█
Total venetoclax cost (DPMQ)	\$█	\$█	\$█	\$█	\$█	\$█
Obinutuzumab scripts (7.4 per course)	█	█	█	█	█	█
Obinutuzumab cost (DPMA)	\$█	\$█	\$█	\$█	\$█	\$█
Patient co-pay (\$14.48) ^b	\$29,556	\$60,058	\$61,048	\$62,034	\$63,010	\$63,975
Net cost of venetoclax + obinutuzumab less copay	\$█	\$█	\$█	\$█	\$█	\$█
Cost offsets due to substitution of existing first line therapies						
Patients substituting from chlorambucil + obinutuzumab (100%)	█	█	█	█	█	█
Chlorambucil + obinutuzumab cost less copay	-\$█	-\$█	-\$█	-\$█	-\$█	-\$█
Cost offsets due to prevention of subsequent anti-leukaemic therapies						

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	Year 1 (2020)	Year 2 (2021)	Year 3 (2022)	Year 4 (2023)	Year 5 (2024)	Year 6 (2025)
Net change in patients initiating R/R therapy	■	■	■	■	■	■
- Ibrutinib monotherapy	■	■	■	■	■	■
- Venetoclax + rituximab	■	■	■	■	■	■
Ibrutinib monotherapy net cost less copay	\$■	-\$■	-\$■	-\$■	-\$■	-\$■
Venetoclax + rituximab net cost less copay	-\$■	-\$■	-\$■	-\$■	-\$■	-\$■
Net cost including cost offsets less copay	\$■	\$■	\$■	\$■	\$■	\$■

Source: Table 114, p.168; Table 121, p.177; Table 122, p.177; Table 123, p.178; Table 126, p.179; Table 132, p.182; Table 137, p.187; Table 141, p.189; Table 142, p.189; Table 143, p.190; Table 144, p.191; Table 147, p.194; Table 148, p.195; Table 149, p.196; Table 150, p.198 of the submission

Abbreviations: CLL, chronic lymphocytic leukaemia; R/R, relapsed/refractory

^a Applied as linear uptake of 7.5% per year over 4 years with adjustments for mortality based on number of years from diagnosis

^b Applied once per treatment course for obinutuzumab (Efficient Funding of Chemotherapy program)

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be less than \$10 million.

6.70 After cost offsets due to substitution of existing first-line therapies and prevention of subsequent anti-leukaemic therapies, the net cost to the PBS for listing venetoclax (proposed effective price) + obinutuzumab (published price) for previously untreated CLL patients was up to less than \$10 million in Year 6, with a cumulative total cost of \$30 - \$60 million over 6 years.

6.71 The ESC agreed with the evaluation that the estimated net cost of venetoclax + obinutuzumab is highly uncertain due to the following issues:

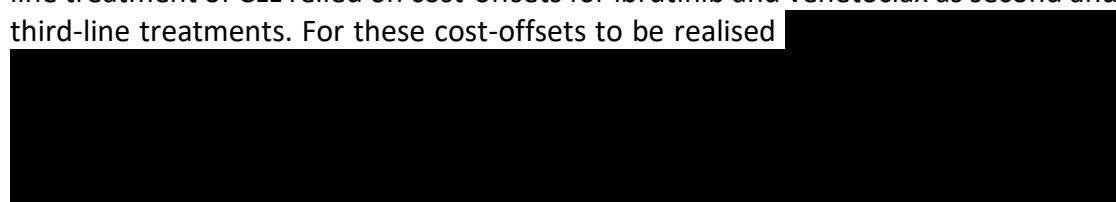
- The estimated population receiving first-line therapy was uncertain due to the assumption of no growth in the incident population over time, poor applicability and reliability of the clinician survey and the inclusion of treated and untreated patients in the prevalent population;
- The submission noted the proposed restriction was broad with potential overlap between the various criteria and assumed that ■% of patients receiving first line therapy would meet eligibility criteria. The size of this population in clinical practice is uncertain, but it is unclear whether the population is under or overestimated;
- The assumption of no market growth due to the listing of venetoclax + obinutuzumab on the PBS was inadequately justified. The PBAC was concerned that there was a risk of leakage and that venetoclax + obinutuzumab could be used in patients who were suitable for fludarabine based chemotherapy;
- Uptake rates of venetoclax were assumed based on a wide range of clinician survey responses, and are highly uncertain;
- The submission's estimate of first line therapy cost offsets assumed 100% of venetoclax + obinutuzumab use would substitute chlorambucil + obinutuzumab based clinician survey responses, and is highly uncertain;

- The submission did not address the impact of availability of ibrutinib as a first line therapy for patients with 17p deletion. Given the emergence of new therapies for patients with cytogenetic aberrations/mutations, it is unclear what effect this will have on venetoclax use in the broader first line setting;
- Cost offsets due to the prevention of relapsed/refractory therapies are likely to be overestimated as it was assumed that these costs are fully avoided, while in practice, it is likely that some of these costs are delayed rather than avoided; and
- The submission did not adequately address the costs associated with the prophylactic management of tumour lysis syndrome (TLS) in patients treated with venetoclax. During the evaluation, these costs were estimated using baseline risk from the CLL-14 trial and hospitalisation costs (between less than \$10 million to less than \$10 million over 6 years).

Financial Management – Risk Sharing Arrangements

6.72 The submission did not propose a risk-sharing arrangement (RSA). However, the submission acknowledged that there are uncertainties associated with the financial estimates and suggested that the sponsor is willing to enter a RSA that would be specific to venetoclax in first line CLL. The sponsor did not consider the impact of a first-line listing on the existing RSA for venetoclax in the relapsed/refractory (R/R) setting.

6.73 The ESC considered that a combined RSA across the first-line and RR settings would be appropriate. The ESC noted that the cost-effectiveness of venetoclax in the first-line treatment of CLL relied on cost-offsets for ibrutinib and venetoclax as second and third-line treatments. For these cost-offsets to be realised



The pre-PBAC also noted that, if recommended for listing, acalabrutinib is also likely to affect the R/R cap.



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

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of venetoclax in combination with obinutuzumab for the first-line treatment of patients with chronic lymphocytic leukaemia (CLL) who have coexisting conditions and are unsuitable for fludarabine

based chemo-immunotherapy. The PBAC accepted that venetoclax + obinutuzumab was clinically superior to current first-line therapy for CLL in delaying progression. However, the PBAC considered that the incremental cost-effectiveness ratio (ICER) was difficult to ascertain based on the model provided and would need to be revised, and the financial estimates were highly uncertain.

- 7.2 The PBAC noted that the comments from consumers and from the Leukaemia Foundation, Lymphoma Australia and Rare Cancers Australia were all in support of the requested listing for venetoclax + obinutuzumab, describing the need for treatment options in CLL patients unable to tolerate the current standard of care.
- 7.3 The PBAC accepted that chlorambucil + obinutuzumab was the appropriate comparator.
- 7.4 The PBAC noted that the submission presented data from a randomised controlled trial, CLL-14, which compared venetoclax + obinutuzumab with the nominated comparator, chlorambucil + obinutuzumab. The PBAC noted that efficacy data were presented for two data-cuts, August 2018 (median follow-up of 29.06 months) and August 2019 (median follow-up not reported).
- 7.5 The PBAC noted that at the August 2018 data-cut the median progression free survival (PFS) was not reached in either arm, but that statistically significantly fewer patients treated with venetoclax + obinutuzumab experienced disease progression or death in the Independent Review Committee (IRC) analysis (HR = 0.33; 95% CI: 0.22, 0.51). The PBAC noted that at the August 2019 data-cut the median PFS was reached in the chlorambucil + obinutuzumab arm (35.6 months) and that the investigator assessed analysis reported similar results to the earlier data-cut (HR = 0.31; 95% CI: 0.22, 0.44).
- 7.6 In terms of time to next anti-CLL treatment (TTNT) following progression, the PBAC noted that although the results statistically significantly favoured venetoclax + obinutuzumab at both data-cuts, there were differences in the post-progression treatment patterns across the treatment groups which were difficult to interpret. The PBAC noted Figure 4 that suggested a large proportion of patients treated with chlorambucil + obinutuzumab experienced delayed or no new anti-CLL treatment after disease progression; whereas, patients treated with venetoclax + obinutuzumab experienced little or no delay. The PBAC considered that it was not unreasonable to expect that patients treated with venetoclax + obinutuzumab would experience a TTNT delay as demonstrated in the chlorambucil + obinutuzumab arm of CLL-14.
- 7.7 The PBAC noted that the trial data demonstrated no additional benefit in terms of OS for venetoclax + obinutuzumab compared to chlorambucil + obinutuzumab. The PBAC considered that OS was not an informative outcome in CLL due to downstream effective treatments and the older mean age at diagnosis (70 years).
- 7.8 The PBAC acknowledged that TTNT was likely a good indicator of treatment effect, however, given the uncertainties with the interpretation of the trial results for this outcome, as identified in section 6 above, and that TTNT was a subjective outcome,

PBAC considered the PFS outcome provided a more robust assessment, using pre-determined criteria at set time points. The PBAC noted the patient reported outcomes did not suggest any substantial decrements to quality of life associated with progression. Overall, the PBAC accepted the clinical claim that venetoclax + obinutuzumab demonstrated superior clinical effectiveness compared to chlorambucil + obinutuzumab in terms of PFS.

- 7.9 The PBAC noted that, unlike the efficacy results, there was no updated safety data from the second data-cut (August 2019). Further, the PBAC noted that venetoclax + obinutuzumab was associated with higher numbers of adverse events, serious adverse events and grade 3/4 adverse event rates (particularly neutropenia) compared to chlorambucil + obinutuzumab. The PBAC considered that overall, whether venetoclax + obinutuzumab was likely to be non-inferior to chlorambucil + obinutuzumab in terms of comparative safety remained uncertain.
- 7.10 The PBAC noted that the submission presented a four-state cost-utility model. The PBAC considered that the cost-effectiveness of venetoclax + obinutuzumab was difficult to ascertain due to uncertainties including:
- the inconsistencies between the TTNT curves in the two arms of the CLL-14 trial. The PBAC considered that, as it was unknown whether the TTNT trial results represented what would happen in clinical practice, use of these data introduced uncertainty into the model. In addition, the model was sensitive to the extrapolation of these curves and the resulting differences in utilities based on the four health states;
 - the use of published utility values, rather than trial based values where available (particularly for the first-line progression free and the progressed but well states);
 - the duration of treatment effect and the appropriate method for reducing this over time (risk versus curve convergence);
 - the use of the Portuguese study to derive health state costs that were considerably higher than those used in previous venetoclax submissions and that did not appear to be clinically valid; and
 - the omission of costs related to the prevention of tumour lysis syndrome (TLS).
- 7.11 The PBAC noted that the ESC recommended a revised base-case that incorporated trial-based utility data for the pre-progression and post-progression health states, included serious adverse event costs, halved the health state costs, included costs related to TLS prophylaxis and applied curve convergence from five years and which resulted in an ICER of \$105,000 - \$200,000 per QALY (August 2018 data-cut data used, using published prices). The pre-PBAC response accepted halving the health state costs, and including serious adverse event costs and costs related to tumour lysis syndrome (TLS) prophylaxis and applied risk, rather than curve convergence from five years, resulting in an ICER of \$45,000 - \$75,000 (August 2018 data-cut).

- 7.12 The PBAC noted that the different patterns across the treatment groups in terms of time from progression to when the next treatment is started (see paragraph 7.6) were included in the model, and the independent extrapolation of PFS and TTNT over the model time horizon further amplified this difference. The PBAC considered a model in which PFS and TTNT were linked would help to ensure the relationship of these outcomes remained clinically valid over the model time horizon, and would allow the impact of different assumptions regarding this relationship to be tested. However, the PBAC acknowledged that the relationship between PFS and TTNT is difficult to determine from the CLL-14 trial and that a revised model would likely need to be informed by external data which would introduce an additional level of uncertainty.
- 7.13 The PBAC considered two possible approaches for assessing the cost-effectiveness of venetoclax + obinutuzumab:
- Use of a new economic model in which PFS and TTNT were linked (as per paragraph 7.12).
 - Revision of the base case model presented in the pre-PBAC response (as per paragraph 7.11) to include a smaller utility decrement for the progressed but well state, together with a lower ICER, to account for the duration of time in this health state being uncertain. The PBAC noted that it had previously accepted a utility decrement in the progressed but well state for obinutuzumab + chlorambucil (March 2015), and that the pre-PBAC response reported a 0.044 utility decrement was observed in the CLL-14 trial between progression free and progressed but well patients. The PBAC considered the trial estimate, subject to evaluation, may be a more appropriate input for the model compared with the 0.08 decrement which was applied in the base case presented in the pre-PBAC response. The PBAC considered for this option an appropriate ICER would be less than \$45,000 - \$75,000 per QALY.
- 7.14 The PBAC noted that the submission had estimated a net cost to the PBS for listing venetoclax (proposed effective price) + obinutuzumab (published price) for previously untreated CLL patients of up to less than \$10 million in Year 6, with a cumulative total cost of \$30 - \$60 million over 6 years. The PBAC noted there were a number of uncertainties with respect to the financial estimates as outlined in paragraph 6.71, and considered the financial impact of the proposed listing was highly uncertain. In addition, the PBAC were concerned that there was a risk of leakage with use in patients who were suitable for fludarabine based chemo-immunotherapy.
- 7.15 Given the high degree of uncertainty in the financial estimates, the PBAC advised that a Risk Sharing Arrangement (RSA) consisting of subsidisation caps would be required to ensure venetoclax + obinutuzumab use in the first-line setting remained cost effective. The PBAC further advised that the RSA include both the proposed first-line and current relapsed/refractory use of venetoclax and ibrutinib for CLL to ensure that the offsets in the existing later-line setting (which are required for the first-line setting to be cost-effective) are realised.

- 7.16 The PBAC considered the requested listing should be revised, consistent with the suggested amendments to the restrictions provided in Section 3.
- 7.17 The PBAC advised that a minor resubmission would be required if the option of revising the pre-PBAC model as outlined in paragraph 7.13 was accepted, and the financial implication estimates and restrictions were adjusted as recommended. A major submission would be required if a new economic model was presented.
- 7.18 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

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

AbbVie welcomes the PBAC's acknowledgement that venetoclax + obinutuzumab is clinically superior to current first-line therapy for CLL however is disappointed with the recommendation to reject the submission. AbbVie will continue to work collaboratively with the PBAC to seek access for patients in need.