

7.14 VENETOCLAX, Tablet 10 mg, 50 mg, 100 mg, Venclexta[®], AbbVie Pty Ltd

1 Purpose of Application

- 1.1 The minor resubmission 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 chlorambucil plus obinutuzumab.
- 1.3 The PBAC has previously considered venetoclax plus obinutuzumab for this indication in March 2020. The submission was not recommended as 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.
- 1.4 Table 1 presents the key components of the resubmission, which remain unchanged.

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

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, p2 of the March 2020 Public Summary Document (PSD)

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 Venetoclax was TGA registered on 5 May 2020 for use in combination with obinutuzumab for the treatment of patients with CLL or small lymphocytic leukaemia (SLL) who are considered unfit or unsuitable for chemo-immunotherapy.
- 2.2 Venetoclax is also TGA registered for use as monotherapy or in combination with rituximab for the treatment of relapsed and/or refractory (RR) CLL.

Public Summary Document – July 2020 PBAC Meeting

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

Previous PBAC consideration

- 2.4 Venetoclax in combination with obinutuzumab was previously considered for this indication by the PBAC at its March 2020 meeting.
- 2.5 A summary of the previous submissions and current submission is provided in the table below.

Public Summary Document – July 2020 PBAC Meeting

Table 2: PBAC outstanding matters of concern with the March 2020 submission and how they are addressed in the current minor resubmission

	PBAC considerations from the March 2020 submission	How the July 2020 minor resubmission addresses the PBACs concerns
Requested PBS listing	The requested listing should be revised, consistent with the suggested amendments (para 7.16)	Accepted, amendments made.
Comparator	Chlorambucil + obinutuzumab was the appropriate comparator (para 7.3)	Unchanged
Clinical claim	Venetoclax + obinutuzumab demonstrated superior clinical effectiveness compared to chlorambucil in terms of PFS (para 7.8). The claim that venetoclax + obinutuzumab was non-inferior to chlorambucil + obinutuzumab was uncertain (para 7.9). The impact of AEs could be explored in the economic model (para 6.42)	Unchanged, no further evidence provided. Unchanged, no further evidence provided; however, the revised economic model evaluated the impact of additional AE costs.
Economic evaluation	The cost-effectiveness of venetoclax + obinutuzumab was difficult to ascertain due to uncertainties including: - inconsistencies between the TTNT curves in the two arms of the CLL-14 trial; - use of published, rather than trial-based, utility values; - risk versus curve convergence; - health state costs that were considerably higher than those used in previous submission; - omission of TLS prevention costs (para 7.10). The PBAC considered the issues could be addressed by either: 1. A new model in which PFS and TTNT were linked; 2. Revision of the model presented in the pre-PBAC response (which halved health state costs, included costs related to TLS, applied risk convergence from 5 years) to include a smaller utility decrement for progressed but well patients and result in an ICER of < \$50,000 per QALY (para 7.13)	Partially accepted. A revised model, based on that presented in the March 2020 pre-PBAC response, was presented which applied a smaller utility decrement for the progressed but well state and resulted in an ICER of \$55,000 to < \$75,000 per QALY (using August 2019 data-cut).
Estimated net cost to PBS	There were a number of uncertainties with respect to the financial estimates and the financial impact was highly uncertain. There was a risk of leakage with use in patients who were suitable for fludarabine based chemo-immunotherapy (para 7.14).	Partially revised. Uptake rates of venetoclax + obinutuzumab were revised. See Table 8 for further details.
RSA	A RSA consisting of subsidisation caps would be required to ensure venetoclax + obinutuzumab use in the first-line setting remained cost effective. The RSA should include both the proposed first-line and current RR use of venetoclax and ibrutinib to ensure that the offsets in the existing later-line setting (which are required for the first-line setting use to be cost-effective) are realised (para 7.15).	Partially accepted. The minor resubmission discussed how a revised RSA that covers both first-line and RR CLL treatments could be implemented.
PBAC decision	Reject	-

AE = adverse event; DPMQ = dispensed price for maximum quantity; ICER = incremental cost-effectiveness ratio; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PFS = progression free survival; QALY = quality adjusted life year; RR relapsed and/or refractory; RSA = risk sharing arrangement; TLS = tumour lysis syndrome; TTNT = time to next treatment
Source: Compiled during the evaluation using March 2020 PBAC Public Summary Document (PSD) and current minor resubmission.

Public Summary Document – July 2020 PBAC Meeting

- 2.6 In March 2020 the PBAC advised that a minor resubmission would be acceptable if the option of revising the pre-PBAC model 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 (paragraph 7.17, venetoclax Public Summary Document (PSD), March 2020). As a new economic model has not been presented, the minor resubmission is appropriate.
- 2.7 A major submission for acalabrutinib for the treatment of previously untreated patients with CLL or SLL considered unsuitable for treatment with a purine analogue (Item 5.01) is also being considered at the July 2020 PBAC meeting.

For more detail on PBAC’s view, see Section 6 PBAC outcome.

3 Requested listing

- 3.1 The requested listing is presented below. The minor resubmission updated the proposed restrictions to incorporate the PBAC Secretariat suggestions from March 2020 and include four restrictions (initial, first continuation, second continuation and dose modification/holding) which correspond to the dosing schedule outlined in the TGA approved Product Information.
- 3.2 The essential elements and proposed published and effective prices remained unchanged compared to March 2020.
- 3.3 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	DPMQ	Available brands
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	NEW (for RSA monitoring) (Existing: 11630D)	1	1	0	Published: \$1,780.45 Effective: \$ [REDACTED]	Venclexta

Category/Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type / Method: <input checked="" type="checkbox"/> Authority Required – <i>immediate/real-time assessment (telephone/online/emergency)</i>
Episodicity: <i>Untreated</i>
Condition: chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Indication: Untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Treatment Phase: Initial treatment in first-line therapy – Dose titration (<i>5-week ramp-up schedule</i>)
Clinical criteria:
The condition must be previously untreated
AND
Clinical criteria:
Patient must be inappropriate for fludarabine based chemo-immunotherapy

Public Summary Document – July 2020 PBAC Meeting

AND
Clinical criteria:
The treatment must be in combination with obinutuzumab <i>during treatment cycle 1 (but not administered on the same days)</i>
AND
Clinical criteria:
Patient must have a creatinine clearance 30 mL/min or greater
AND
Clinical criteria:
Patient must have a total cumulative illness rating scale (CIRS) score of greater than 6 (excluding CLL-induced illness or organ damage); or
Patient must have a creatinine clearance less than 70 mL/min
AND
Clinical criteria:
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.
<i>The treatment must be once in a lifetime with this drug for this condition</i>
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	DPMQ	Available brands
VENETOCLAX (CONTINUING TREATMENT) venetoclax 100 mg tablet, 120	NEW	1	120	4	Published: \$7,775.14 Effective: \$ [REDACTED]	Venclexta

Category/Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type / Method: <input checked="" type="checkbox"/> Authority Required – <i>immediate/real-time assessment (telephone/online/emergency)</i>
Condition: chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Treatment Phase: First continuing treatment (treatment cycles 2 to 6 inclusive) of first-line therapy
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
The treatment must be in combination with obinutuzumab (refer to Product Information for timing of obinutuzumab)
AND
Prescriber instructions Clinical criteria:
The treatment must be ceased upon disease progression. The treatment must cease to be a PBS benefit upon disease progression
AND
Clinical criteria:
<i>The treatment must be once in a lifetime with this drug for this condition</i>
AND
Clinical criteria:
<i>The treatment must not be prescribed under this restriction within 14 days of having prescribed the starting pack for initial treatment</i>
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.

Public Summary Document – July 2020 PBAC Meeting

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	DPMQ	Available brands
VENETOCLAX (CONTINUING TREATMENT) venetoclax 100 mg tablet, 120	NEW	1	120	5	Published: \$7,775.14 Effective: \$ [REDACTED]	Venclexta

Category/Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type/ Method: <input checked="" type="checkbox"/> Authority Required – <i>immediate/real-time assessment (telephone/online/emergency)</i>
Condition: chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Treatment Phase: Second and final continuing treatment <i>prescription</i> (treatment cycles 7 to 12 inclusive) of first-line therapy
Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Prescriber instruction Clinical criteria: 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.
<i>The treatment must cease to be a PBS benefit upon disease progression; or</i>
<i>The treatment must cease to be a PBS benefit upon completion of 12 cycles of treatment with this drug for this condition, whichever (disease progression/12 cycles) comes first</i>
AND
Clinical criteria: <i>The treatment must be once in a lifetime with this drug for this condition</i>
AND
Clinical criteria: <i>The treatment must not be prescribed under this restriction before having administered cycle 6 of treatment</i>
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	DPMQ	Available brands
VENETOCLAX (DOSE HOLD PACK) venetoclax 10 mg tablet, 14	11624T	1	14	0	Published: \$107.11 Effective: \$ [REDACTED]	Venclexta
venetoclax 50 mg tablet, 7	11648C	1	7	0	Published: \$252.61 Effective: \$ [REDACTED]	

Category/Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type/ Method: <input checked="" type="checkbox"/> Authority Required – <i>immediate/real-time assessment (telephone/online/emergency)</i>
Condition: chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Treatment phase: Dose modification requirement
Clinical criteria: The treatment must be for dose titration purposes
AND
Clinical criteria: Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition

Public Summary Document – July 2020 PBAC Meeting

<i>The treatment must cease to be a PBS benefit upon disease progression; or</i>
<i>The treatment must cease to be a PBS benefit upon completion of 12 cycles of treatment with this drug for this condition, whichever (disease progression/12 cycles) comes first</i>
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.

- 3.4 The minor resubmission acknowledged that flow-on changes would be required to the current listings for obinutuzumab to allow use with venetoclax (as it currently specifies that obinutuzumab should only be used with chlorambucil). In March 2020, the Secretariat proposed a new, separate restriction for obinutuzumab for use in combination with venetoclax. The PBAC considered that a separate restriction, which has 8 repeats (the current listing has 7 repeats) to reflect the dosing regimen outlined in the venetoclax TGA approved Product Information and remains silent on CD20 positivity was appropriate.

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	№.of Rpts	Manufacturer
OBINUTUZUMAB Injection	NEW (Public) NEW (Private)	1,000 mg	8	Roche Products Pty Ltd
Available brands				
Gazyva (obinutuzumab 1 g/40 mL injection, 40 mL vial)				

Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Private hospitals code)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type / Method: <input checked="" type="checkbox"/> Authority Required – Streamlined (new 4 or 5 digit code)
Indication: Untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
Treatment Phase: For combination use with venetoclax treatment cycles 1 to 6 inclusive
Clinical criteria:
<i>The condition must be previously untreated</i>
AND
Clinical criteria:
<i>The treatment must be in combination with PBS-subsidised venetoclax</i>
Administrative Advice: A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.

- 3.5 The PBAC reiterated that CLL and SLL are essentially the same disease, and therefore considered that the indication should be amended to include SLL.

- 3.6 The PBAC noted that Authority Required – immediate/real-time assessment (telephone/online) listings are consistent with the existing venetoclax and ibrutinib RR CLL listings.

- 3.7 Consistent with previous considerations to list ofatumumab and obinutuzumab for first-line CLL, the PBAC did not propose a definition for the clinical criterion “Patient must be inappropriate for fludarabine based chemo-immunotherapy”.
- 3.8 The TGA approved Product Information recommends that venetoclax + obinutuzumab is administered for a finite duration (12 cycles/months) or ceased upon disease progression. Therefore, the restrictions propose limiting treatment to 12 months treatment or cessation of treatment upon disease progression, whichever comes first, in the second continuing restriction. The PBAC considered this was appropriate.
- 3.9 The Secretariat suggested the addition of clinical criteria that prevent prescribers from seeking authority approval for the entire treatment course at the beginning of treatment (under ‘convenience/efficiency of administration tasks’ reasons). The July 2020 pre-PBAC response proposed removing the time restriction relating to the first continuing treatment as the proposed wording would require an additional hospital visit for the sole purpose of obtaining the prescription. The PBAC considered this was appropriate.
- 3.10 The July 2020 pre-PBAC response suggested the clinical criterion in the initial treatment (dose titration) restriction that specifies treatment with venetoclax must be in combination with obinutuzumab should read as “The treatment must be in combination with obinutuzumab (refer to Product Information for timing of obinutuzumab and venetoclax)”. It stated that this directs clinicians to the Product Information for correct dosing instructions, and is consistent with wording suggested for the first continuing restriction. The PBAC considered this was appropriate.
- 3.11 The July 2020 pre-PBAC response also argued that once in a lifetime access to venetoclax is covered by the existing RR CLL restriction criterion, “Patient must not have previously received PBS-subsidised treatment with this drug for this condition”. The PBAC considered this was appropriate.

For more detail on PBAC’s view, see Section 6 PBAC outcome.

4 Comparator

- 4.1 The previous major submission considered by the PBAC in March 2020 nominated chlorambucil in combination with obinutuzumab as the comparator. This was unchanged. The PBAC previously accepted that chlorambucil + obinutuzumab was the appropriate comparator (paragraph 7.3, venetoclax PSD, March 2020).

For more detail on PBAC’s view, see Section 6 PBAC outcome.

5 Consideration of the evidence

Sponsor hearing

- 5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 5.2 The PBAC noted and welcomed the input from individuals (13) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with the combination therapy of venetoclax + obinutuzumab including an improved quality of life, high rates of remission and few side effects.
- 5.3 The PBAC noted the advice received from the Leukaemia Foundation detailing the high unmet clinical need for treatments in patients who are unable to tolerate the current standard of care.

Clinical trials

- 5.4 The key trial in the March 2020 submission was CLL-14, a direct, head-to-head, randomised comparison of venetoclax + obinutuzumab versus chlorambucil + obinutuzumab in previously untreated patients with CLL and coexisting medical conditions.
- 5.5 No new clinical evidence for venetoclax + obinutuzumab was presented in the minor resubmission.

Comparative effectiveness

- 5.6 The PBAC previously considered that venetoclax + obinutuzumab was clinically superior to current first-line CLL therapies in delaying progression (paragraph 7.1, venetoclax PSD, March 2020). Overall, the PBAC accepted venetoclax + obinutuzumab demonstrated superior clinical effectiveness compared to chlorambucil + obinutuzumab in terms of PFS (paragraph 7.9, venetoclax PSD, March 2020).
- 5.7 A summary of the key efficacy events are presented below.

Table 3: Summary of the key efficacy outcomes from CLL-14

	Venetoclax + obinutuzumab (N=216)	Chlorambucil + obinutuzumab (N=216)
PFS, IRC-assessed (17 August 2018 data-cut)		
Patients with event, n (%)	29 (13.4%)	79 (36.6%)
Median time to event, months (95% CI)	NE	NE (31.1, NE)
Stratified HR (95% CI)	0.33 (0.22, 0.51)	
PFS, INV-assessed (23 August 2019 data-cut)		
Patients with event, n (%)	42 (19.4%)	113 (52.3%)
Median time to event, months (95% CI)	NE	35.6 (33.7, 40.7)
Stratified HR (95% CI)	0.31 (0.22, 0.44)	
OS (23 August 2019 data-cut)		
Patients with event, n (%)	27 (12.5%)	27 (12.5%)
Median time to event, months (95% CI)	NE	NE
Stratified HR (95% CI)	1.03 (0.60, 1.75)	
TTNT (17 August 2018 data-cut)		
Patients with event ^a , n (%)	27 (12.5%)	45 (20.8%)
Median time to event, months (95% CI)	NE	NE (34.6, NE)
Stratified HR (95% CI)	0.60 (0.37, 0.97)	
TTNT (23 August 2019 data-cut)		
Patients with event ^a , n (%)	35 (16.2%)	66 (30.6%)
Median time to event, months (95% CI)	NE	NE
Stratified HR (95% CI)	0.51 (0.34, 0.78)	

CI = confidence interval; CLL = chronic lymphocytic leukaemia; CRR = complete response rate; HR = hazard ratio; INV = investigator; IRC = independent review committee; OS = overall survival; PFS = progression free survival; TTNT = time to next treatment

Source: Table 5, p11 of the minor resubmission

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

- 5.8 At the August 2019 data-cut, median PFS was reached in the chlorambucil + obinutuzumab arm (35.6 months) and the investigator assessed analysis reported that statistically significantly fewer patients treated with venetoclax + obinutuzumab experienced disease progression (HR = 0.31; 95% CI: 0.22, 0.44). Similar results were observed at the August 2018 data-cut for both the investigator (HR = 0.35; 95% CI: 0.21, 0.53) and independent review committee (HR = 0.33; 95% CI: 0.22, 0.51) assessed results.
- 5.9 In terms of time to next anti-CLL treatment (TTNT) following progression, although the results statistically significantly favoured venetoclax + obinutuzumab, there were differences in the post-progression treatment patterns across the treatment groups that were difficult to interpret. In March 2020 the PBAC noted that 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 (paragraph 7.6, venetoclax PSD, March 2020).
- 5.10 The pre-PBAC response provided a summary of the August 2019 data relative to the August 2018 data. The PBAC noted that, using the August 2019 data-cut, the stratified

PFS HR decreased from 0.35 (95% CI: 0.23, 0.53) to 0.31 (95% CI: 0.22, 0.44) (for the investigator assessed results); TTNT HR decreased from 0.60 (95% CI: 0.37, 0.97) to 0.51 (95% CI: 0.34, 0.78); and the OS HR decreased from 1.24 (95% CI: 0.64, 2.4) to 1.03 (95% CI: 0.60, 1.75).

Comparative harms

- 5.11 A claim of non-inferior safety between venetoclax + obinutuzumab and chlorambucil + obinutuzumab in the March 2020 submission was based on adverse event data from the CLL-14 trial after a median follow-up of 28.1 months. The results are summarised below.
- 5.12 The PBAC previously considered that the claim of non-inferior safety was uncertain as 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 (paragraph 7.9, venetoclax PSD, March 2020).

Table 4: Summary of key AEs in CLL-14 (safety population; August 2018 data-cut)

AEs, n (%) [# events]	Venetoclax + obinutuzumab (N=212)	Chlorambucil + obinutuzumab (N=214)	RR (95% CI)	RD (95% CI)
Patients with ≥ 1 AE	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 AEs	4 (1.9%)	1 (0.5%)	4.04 (0.46, 35.8)	0.01 (-0.01, 0.04)
Serious AEs 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 AEs	167 (78.8%) [344 events]	164 (76.6%) [239 events]	1.03 (0.93, 1.14)	0.02 (-0.06, 0.10)
AEs 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)

AE = adverse event; CI = confidence interval; CLL = chronic lymphocytic leukaemia; RD = risk difference; RR = relative risk

Source: Table 7, p18 of the March 2020 PBAC Public Summary Document

- 5.13 The minor resubmission again claimed that venetoclax + obinutuzumab is non-inferior to chlorambucil + obinutuzumab in terms of comparative safety.
- 5.14 The minor resubmission stated that venetoclax + obinutuzumab delays or prevents the need for subsequent anti-CLL treatments which would therefore delay or avoid the risk of adverse events associated with subsequent treatments. The resubmission claimed that it would be reasonable to expect the overall risk of adverse events treated with venetoclax + obinutuzumab in the first-line setting will be more favourable than patients treated with chlorambucil + obinutuzumab who progress to next line therapy.

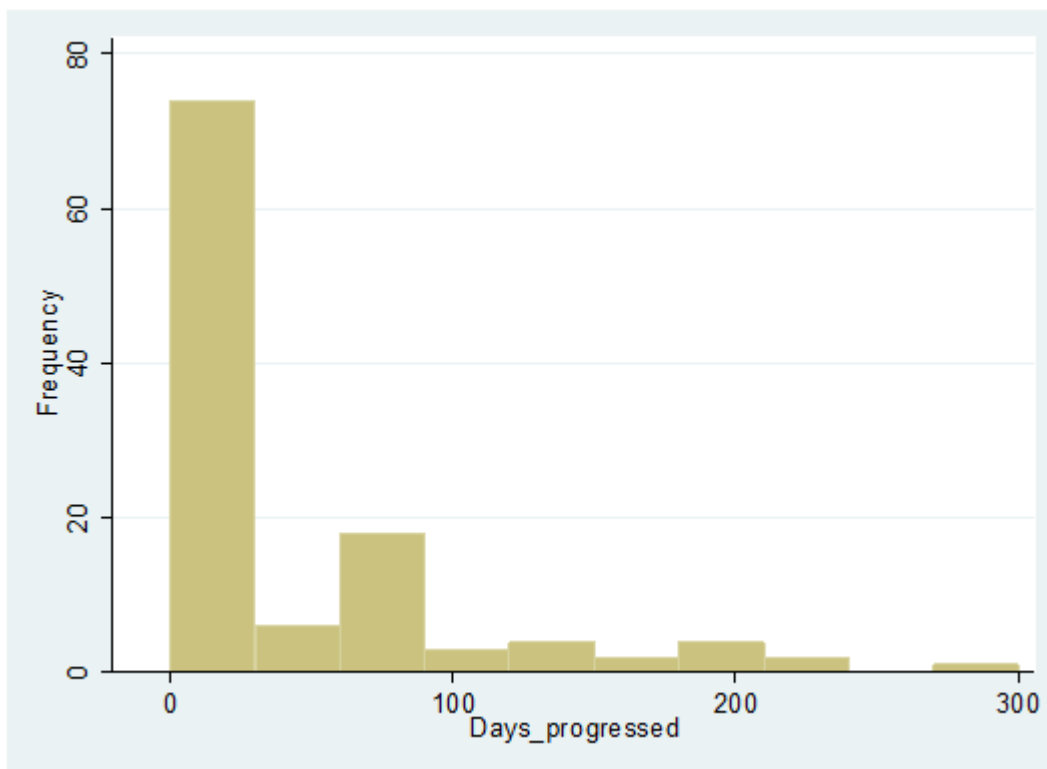
Clinical claim

- 5.15 The clinical claims remained unchanged, with the minor resubmission stating that venetoclax + obinutuzumab is superior in terms of comparative effectiveness and non-inferior in terms of comparative safety to chlorambucil + obinutuzumab.
- 5.16 The PBAC considered that the claim of non-inferior comparative safety remained uncertain.

Economic analysis

- 5.17 The minor resubmission presented a revised cost-utility analysis, using the base case proposed in the March 2020 pre-PBAC response and applying a smaller utility decrement to the progressed but well health state.
- 5.18 The sponsor noted that in March 2020 the PBAC suggested that a new economic model in which PFS and TTNT were linked as an alternate option. The minor resubmission stated that a link between PFS and TTNT would allow for different assumptions surrounding the link to be tested; however, these assumptions and the use of external data to populate the model may exacerbate any uncertainty. The minor submission stated that the internal validity of the randomised controlled trial was the best source of evidence upon which to base the economic model.
- 5.19 The base case economic model proposed in the March 2020 pre-PBAC response, which included serious adverse event costs, halved the health state costs, included costs related to TLS prophylaxis and applied risk convergence from five years, resulted in an ICER of \$55,000 to < \$75,000 per QALY when using the August 2018 data-cut and of \$55,000 to < \$75,000 per QALY when using the August 2019 data-cut. In March 2020 the PBAC considered that the application of a smaller utility decrement for the progressed but well state, together with an ICER of less than \$50,000 per QALY, would account for the duration of time in this health state being uncertain (paragraph 7.13, venetoclax PSD, March 2020).
- 5.20 In March 2020, the PBAC noted that a utility decrement of 0.044 was derived from the CLL-14 trial for the progressed but well health state. The March 2020 submission and the March 2020 pre-PBAC response applied a decrement of 0.080, which was based on a published study of CLL patients in the UK by Kosmas 2015.
- 5.21 The minor resubmission stated that the trial data for the 0.044 utility decrement was not complete, and that the CLL-14 trial did not routinely collect utility data after patients had progressed. In addition, the majority of post progression utility data were collected within 90 days of reported disease progression – see Figure 1. As the average time spent in the progressed but well health state in the economic model was over two years, the minor resubmission stated that the trial-based utility decrement was only applicable for a short time following progression and was not representative of the entire time spent in the health state.

Figure 1: Timing of collection of EQ-5D data following progression in CLL-14



Source: Figure 1, p19 of the minor resubmission

- 5.22 The minor resubmission stated that the utility decrement of 0.080 in the progressed but well health state reflected a gradual (linear) decline from a utility value of 0.82 in the progression free health state to 0.66 in the progressed disease health state. In addition, a decrement of 0.044 early in the course of the progressed but well health state was consistent with an average utility decrement of 0.080 over the entire period of time spent in this state.
- 5.23 The results of the economic model when a utility decrement of 0.044 was applied to the progressed but well health state are presented below.
- 5.24 The economic model provided with the March 2020 submission utilised clinical data from the August 2018 data-cut. The model provided with the March 2020 pre-PBAC response utilised clinical data from the August 2019 data-cut. The August 2019 data has not been independently verified. The July 2020 pre-PBAC response stated that the August 2019 data represented the most up to date information and that although the August 2019 data had not been evaluated within the model, the March 2020 evaluation considered that the updated data appeared to be consistent with the extrapolated survival curves. The July 2020 pre-PBAC response also stated that the results of the model using the August 2019 data-cut were slightly improved relative to the August 2018 data-cut as the TTNT curves were further separated.

Public Summary Document – July 2020 PBAC Meeting

Table 5: Results of the economic analysis applying differing utility decrements in the progressed but well health state

	March 2020 pre-PBAC response	July 2020 minor resubmission
Utility decrement in progressed but well health state	0.080	0.044
ICER (\$/QALY) at proposed price (base case)		
August 2018 data-cut	\$55,000 to < \$75,000	\$75,000 to < \$95,000
August 2019 data-cut*	\$55,000 to < \$75,000	\$55,000 to < \$75,000
Price reduction required for \$50,000 ICER#		
August 2018 data-cut	█%	█%
August 2019 data-cut*	█%	█%

ICER = incremental cost-effectiveness ratio; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality adjusted life year

Source: Table 6, p15 of the minor resubmission and PBAC_Section 3_CUA_VTX+Obi_Minor – Excel document

* Data from the August 2019 data-cut was not used in the original March 2020 submission's economic model. Therefore it has not been independently evaluated.

Price reduction applied to continuing pack AEMP of \$█ only

- 5.25 The base case proposed in the minor resubmission which utilises clinical data from the August 2019 data-cut and a utility decrement for the progressed but well health state of 0.08 results in an ICER of \$55,000 to < \$75,000 per QALY gained. This is the same scenario as provided in the pre-PBAC response to the March 2020 submission.
- 5.26 Application of a 0.044 utility decrement to the March 2020 pre-PBAC model resulted in an ICER of \$55,000 to < \$75,000 using the August 2019 data-cut and \$75,000 to < \$95,000 using the August 2018 data-cut.
- 5.27 The minor resubmission acknowledged that the ICERs presented above were not less than \$50,000 per QALY, as requested by the PBAC in March 2020. The minor resubmission stated that as the analyses already represent a highly conservative base case, a price reduction for venetoclax was not proposed.
- 5.28 In addition, the minor resubmission reiterated that the treatment cost of venetoclax is fixed as it is given for a fixed duration (12 months). The July 2020 pre-PBAC response argued that the proposed price already represented an approximate 50% reduction in the cost per patient relative to the cost of venetoclax in RR CLL because of the shorter treatment duration (12 months versus 24 months).
- 5.29 The PBAC noted that despite the claim of non-inferior safety, the March 2020 pre-PBAC economic model included a cost of \$█ per patient in the venetoclax + obinutuzumab arm to account for serious adverse events. Removing this cost and using the utility decrement of 0.08 reduces the ICER to \$55,000 to < \$75,000 per QALY using the August 2019 data-cut and to \$55,000 to < \$75,000 per QALY using the August 2018 data-cut.
- 5.30 The costs applied in the economic model per patient in the RR setting were based on █ months (█ units) of ibrutinib treatment (using effective DPMQ of \$█). However, the minor resubmission stated that the actual utilisation of ibrutinib per patient was likely to be longer than █ months, citing Byrd et al, 2019, which suggested that the actual average duration of time of ibrutinib was 41 months. As

Public Summary Document – July 2020 PBAC Meeting

demonstrated in the table below, increasing the RR setting costs per patient had a large effect on the ICER.

Table 6: Results of the economic analysis with increasing costs per patient treated for RR disease

	March 2020 pre-PBAC response	July 2020 minor resubmission
Utility decrement	0.080	0.044
ICER (base case: RR costs = \$ [redacted]/patient) August 2018 data-cut August 2019 data-cut*	\$ [redacted]	\$ [redacted]
ICER (RR costs = \$ [redacted], i.e. 25% increase) August 2018 data-cut August 2019 data-cut*	\$ [redacted]	\$ [redacted]
ICER (RR costs = \$ [redacted], i.e. 50% increase) August 2018 data-cut August 2019 data-cut*	\$ [redacted]	\$ [redacted]
ICER (RR costs = \$ [redacted], i.e. 41 months ibrutinib) August 2018 data-cut August 2019 data-cut*	\$ [redacted]	\$ [redacted]

AE = adverse event; ICER = incremental cost-effectiveness ratio; PBAC = Pharmaceutical Benefits Advisory Committee; RR = relapsed and/or refractory

Source: Table 7, p17 of the minor resubmission and PBAC_Section 3_CUA_VTX+Obi_Minor – Excel document

* Data from the August 2019 data-cut was not used in the original March 2020 submission’s economic model. Therefore it has not been independently evaluated.

The redacted table shows ICERs in the range of \$0 to < \$5,000 to \$75,000 to < \$95,000.

Drug cost/patient/course:

5.31 Drug costs per patient for venetoclax + obinutuzumab versus chlorambucil + obinutuzumab remained unchanged from the March 2020 submission. Costs 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.

Public Summary Document – July 2020 PBAC Meeting

Table 7: 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: 8.67 ^f	7.355 ^g	3.784 ^h	7.464 ⁱ
Cost/script	Initial: \$ [REDACTED] (effective DPMQ) Continuing: \$ [REDACTED] (effective DPMQ)	\$5,458.99 (weighted published DPMA) ^j	\$133.63 (published DPMQ)	\$5,458.99 (weighted published DPMA) ^j
Cost/patient/course ^k	\$ [REDACTED]	\$40,151	\$506	\$40,746
Total cost/patient/course	\$ [REDACTED]			\$41,252

Source: Table 16, p33 of the March 2020 PBAC PSD

^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 / 1,000 mg (recommended dose per administration)

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

ⁱ Mean cumulative dose / 1,000 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

5.32 The table below presents the main issues identified by the PBAC with the utilisation and financial impact estimates provided in the March 2020 submission and how they have been addressed in the July 2020 minor resubmission.

Table 8: Issues identified with the March 2020 financial estimates and how they have been addressed in the July 2020 minor resubmission

Variable	Input	Source	How issue has been addressed in the July 2020 minor resubmission
CLL incidence rate	6.7 per 100,000	AIHW 2019	<p>Unchanged from March 2020.</p> <p>In March 2020 the PBAC noted that the submission applied a constant incidence rate.</p> <p>The minor resubmission stated that AIHW data indicates no definite trend in CLL incidence, with reported rates experiencing minor shifts in both directions over the last 10 years. The resubmission stated that a constant rate ensures patient numbers are not overestimated.</p> <p>In addition, there is no prevalent population, instead a delay in incident patients is applied for 30% of patients. As a watch and wait approach is often taken for CLL patients 30% of patients were determined to initiate treatment immediately, 30% initiate treatment within 5 years (7.5 in years 2 to 5), and 40% never initiate treatment.</p>

Public Summary Document – July 2020 PBAC Meeting

Variable	Input	Source	How issue has been addressed in the July 2020 minor resubmission
Market growth	Nil	Assumption	<p>Unchanged from March 2020.</p> <p>In March 2020 the PBAC considered the assumption of no market growth inadequately justified and were concerned that there was a risk of leakage, with venetoclax + obinutuzumab being used in patients who were suitable for fludarabine based treatments.</p> <p>The minor resubmission stated that the assumption of no market growth was an effective way of limiting the financial exposure in any potential RSA.</p>
Proportion of patients unsuitable for fludarabine based chemo-immunotherapy	65%	Clinician advice	<p>Unchanged from March 2020.</p> <p>In March 2020 the PBAC were unclear whether this population was under or over estimated.</p> <p>The minor resubmission acknowledged that the proportion of first-line patients assessed as unsuitable for fludarabine based treatment was uncertain.</p>
Uptake of venetoclax + obinutuzumab	90% annually	Reflects potential use of venetoclax + obinutuzumab within the proposed restriction	<p>Increased from 31% in Year 1 and 62% in Years 2 to 6 in March 2020.</p> <p>In March 2020 the PBAC considered the uptake rates to be highly uncertain.</p> <p>The minor resubmission stated that a rate of 90% was reasonable as venetoclax + obinutuzumab represented the most efficacious treatment option. The minor resubmission applied a full year of costs to all patients in Year 1 of listing. The PBAC considered that the uptake rate in Year 1 was overestimated.</p>
Substitution of chlorambucil + obinutuzumab	100%	Assumption	<p>Unchanged from March 2020.</p> <p>In March 2020 the PBAC noted that 100% of the patients estimated to receive venetoclax + obinutuzumab would be substituting chlorambucil + obinutuzumab.</p> <p>The minor resubmission acknowledged that this was uncertain, as other therapies are available to these patients.</p>
Proportion of patients initiating RR treatment each year after initiating first-line treatment Year 1 Year 2 Year 3 Year 4 Year 5 Year 6	Ven + Obi 1.9% 1.9% 1.6% 1.8% 1.7% 6.6%	Chl + Obi 2.8% 8.2% 8.0% 6.9% 6.1% 5.5%	<p>Derived from the economic model. Reflects extrapolation of RCT evidence after 3.5 years^a.</p> <p>Unchanged from March 2020.</p> <p>In March 2020 the PBAC noted that cost offsets due to the prevention of RR therapies are likely to be overestimated as it was assumed that they were fully avoided, whereas in practice, it is likely that some costs would be delayed, rather than avoided.</p> <p>The minor resubmission stated that the cost offsets are true to the trial data and make no assumptions about whether the costs are ultimately delayed or avoided, just that they are not accrued within the 6-year analysis.</p>

Public Summary Document – July 2020 PBAC Meeting

Variable	Input	Source	How issue has been addressed in the July 2020 minor resubmission
Impact of ibrutinib availability in the first line setting for patients with 17p deletion	Nil		Unchanged from March 2020. In March 2020 the PBAC noted that the impact of the availability of ibrutinib in the first-line setting was not addressed. The minor resubmission stated that as limited details regarding ibrutinib were available, it was impractical to account for its use in the financial estimates. The MSW indicated that the process for listing ibrutinib was considered inactive as the sponsor had not advised whether they intend to proceed or not within 60 days of receiving the ratified PBAC minutes.
Costs associated with TLS prophylaxis.	\$1,222 per patient	From economic model	Not applied to budget impact model. In March 2020 the PBAC noted that costs associated with TLS prophylaxis were not addressed in the financial estimates. The minor resubmission added a cost per patient for hospitalisation associated with TLS prophylaxis, which is accrued to state and private hospital budgets.

AIHW = Australian Institute of Health and Welfare; Chl = chlorambucil; CLL = chronic lymphocytic leukaemia; MSW = Medicine Status Website; Obi = obinutuzumab; PBAC = Pharmaceutical Benefits Advisory Committee; RCT = randomised controlled trial; RR = relapsed and/or refractory; RSA = risk sharing arrangement; TLS = tumour lysis syndrome; Ven = venetoclax

Source: Table 9, p24 of the minor resubmission

^a Interpretation: If 1,000 patients are treated first line with Ven + Obi (or Chl + Chl) in Year 1, then 16 (i.e. 1.6%) (or 80, 8.0%) are predicted to commence RR treatment in Year 3.

5.33 The revised utilisation and financial impact estimates associated with the potential first-line listing of venetoclax + obinutuzumab on the PBS/RPBS are presented in the table below.

Public Summary Document – July 2020 PBAC Meeting

Table 9: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of venetoclax + obinutuzumab						
Total eligible patients	█	█	█	█	█	█
Number of patients treated (90% uptake)	█	█	█	█	█	█
March 2020 - Number of patients treated	█	█	█	█	█	█
Venetoclax initial scripts (1 per course)	█	█	█	█	█	█
Venetoclax continuing scripts (8.7 per course)	█	█	█	█	█	█
Obinutuzumab scripts (7.4 per course)	█	█	█	█	█	█
Estimated cost of venetoclax + obinutuzumab						
Cost of venetoclax	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Cost of obinutuzumab	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Patient co-pay (\$14.48) ^a	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Total cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
March 2020 – Total cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Cost offsets due to substitution of existing first-line therapies						
Patients substituting from Chl + Obi (100%)	█	█	█	█	█	█
Cost of Chl + Obi less co-pay	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Cost offsets due to reduced use of RR therapies						
Change in patients initiating RR therapy	█	█	█	█	█	█
- Ibrutinib	█	█	█	█	█	█
- Venetoclax + rituximab	█	█	█	█	█	█
Cost of ibrutinib less co-pay	\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Cost of venetoclax + rituximab less co-pay	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Net financial implications to the PBS/RPBS						
Net cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
March 2020 – Net cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

Chl = chlorambucil; Obi = obinutuzumab; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; RR = relapsed and/or refractory

Source: Table 10, p25 of the minor resubmission and PBAC_Section 4_BIM_VTX+Obi_MINOR – Excel workbook

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

5.34 The minor resubmission estimated that the addition of venetoclax + obinutuzumab to the PBS/RPBS would result in a net cost of \$10 million to < \$20 million in Year 1, \$0 to < \$10 million in Year 6 and total \$70 million to < \$80 million over the first six years. The increase in cost compared to the March 2020 submission was primarily related to the increase in the assumed uptake rate of venetoclax + obinutuzumab from 31% in Year 1 and 62% in Years 2 to 6 to 90% in Years 1 to 6.

- 5.35 The July 2020 pre-PBAC response stated that the lower uptake rates applied in the March 2020 submission reflected a circumstance where ibrutinib and other competing treatments would also be available. The PBAC considered the revised uptake rate of 90% was appropriate for Year 2 onwards. A lower (potentially 45%) uptake rate was recommended for Year 1 to account for patients not receiving a full course of treatment of venetoclax and obinutuzumab in the first year of listing.
- 5.36 The PBAC considered that the number of venetoclax continuing scripts and obinutuzumab scrips (as shown above in Table 9) should be less in the first year, as not all patients would commence treatment at the start of the year.

Financial management - risk sharing arrangements

- 5.37 In March 2020, the PBAC advised that any proposed RSA should include both the first-line and current RR 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 use to be cost-effective) are realised (paragraph 7.15, venetoclax PSD, March 2020).
- 5.38 In the minor resubmission the sponsor stated that it accepted that any future RSA would link to savings in RR treatment which are intrinsic to the cost-effectiveness of venetoclax in the first-line setting and considered that the financial analysis presented above would form the basis for such a proposal. [REDACTED]

- 5.39 The sponsor considered that in such an arrangement, [REDACTED]

- 5.40 The minor resubmission noted that in the current RSA the effective cost per patient of ibrutinib is [REDACTED] packs ([REDACTED] months); however, the average treatment duration of ibrutinib may reach [REDACTED] packs ([REDACTED] months).

- 5.41 The minor submission and pre-PBAC response discussed different approaches for the RSA, [REDACTED]

For more detail on PBAC's view, see Section 6 PBAC outcome.

6 PBAC Outcome

- 6.1 The PBAC recommended the Authority Required 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

Public Summary Document – July 2020 PBAC Meeting

based chemo-immunotherapy. The PBAC was satisfied that venetoclax + obinutuzumab provides, for some patients, an improvement in efficacy over current first-line therapies in delaying progression.

- 6.2 The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of venetoclax + obinutuzumab would be acceptable at the price proposed in the minor resubmission given the fixed 12-month treatment duration, and with a Risk Sharing Arrangement (RSA) that ensures the reduced use of treatments in the existing later-line setting are realised.
- 6.3 The PBAC noted that the comments from consumers were in support of the requested listing, describing a range of benefits of treatment with the combination therapy of venetoclax + obinutuzumab including an improved quality of life and high rates of remission.
- 6.4 In terms of the revised restriction presented in Section 3, the PBAC noted that the July 2020 pre-PBAC response had accepted most of the suggested amendments. The PBAC also noted that the response proposed further changes, as outlined in paragraphs 3.9 to 3.11, and considered these were appropriate.
- 6.5 The PBAC reiterated its previous advice that chlorambucil + obinutuzumab was the appropriate comparator.
- 6.6 The PBAC noted that no new clinical evidence for venetoclax + obinutuzumab was presented in the minor resubmission. The PBAC considered that the results observed at the August 2019 data-cut were consistent with those observed at the August 2018 data-cut. The PBAC reiterated its previous consideration that, overall, venetoclax + obinutuzumab demonstrated superior clinical effectiveness compared to chlorambucil + obinutuzumab in terms of progression free survival (PFS).
- 6.7 With no new data presented in the resubmission, the PBAC reiterated its previous consideration that, overall, the non-inferior comparative safety claim of venetoclax + obinutuzumab versus chlorambucil + obinutuzumab remained uncertain. In addition, the PBAC noted that serious adverse event costs were applied to the venetoclax + obinutuzumab arm of the revised economic model.
- 6.8 The PBAC noted that the minor resubmission, as previously requested, presented a revised cost-utility analysis using the base case proposed in the March 2020 pre-PBAC response and applying a smaller utility decrement to the progressed but well health state (0.044 versus 0.080). This resulted in an ICER of \$55,000 to < \$75,000 per QALY (using the August 2019 data cut). The PBAC noted that the ICER was not less than \$50,000 per QALY as previously requested; however, accepted the sponsor's arguments regarding aspects of the modelling being potentially conservative, including the reduced utility decrement for the progressed but well state and excluding adverse event costs for RR treatments. The PBAC also considered that the fixed 12 month treatment duration of venetoclax mitigated some of the uncertainty

regarding the treatment cost per patient. The PBAC therefore considered that the cost-effectiveness of venetoclax + obinutuzumab would be acceptable at the price proposed in the minor resubmission, when the offsets for use in the RR setting can be realised.

- 6.9 The PBAC noted that the minor resubmission had estimated a net cost to the PBS for listing venetoclax (proposed effective price) + obinutuzumab (published price) for previously untreated CLL patients of \$10 million to < \$20 million in Year 1, \$0 million to < \$10 million in Year 6, and with a cumulative total cost of \$70 million to < \$80 million over the first six years. The PBAC noted this was an increase in cost compared to the March 2020 submission, primarily related to the increase in assumed uptake rate of venetoclax + obinutuzumab from 31% in Year 1 and 62% in Years 2 to 6 to 90% in Years 1 to 6. The PBAC considered the revised uptake rate of 90% was appropriate for Year 2 onwards, but that the rate in Year 1 should be reduced to account for patients not receiving a full course of treatment of venetoclax and obinutuzumab in the first year of listing.
- 6.10 The PBAC noted the sponsors concerns regarding the structure of the RSA in the RR CLL setting, but reiterated its previous advice that an RSA consisting of expenditure caps would be required to ensure venetoclax + obinutuzumab use in the first-line setting remained cost-effective. The PBAC further advised that the new RSA needs to ensure that the cost offsets in the existing RR setting (which are required for the first-line setting to be cost-effective) are realised in practice. The PBAC noted that in its pre-PBAC response the sponsor had proposed a methodology to ensure the offsets are realised outside the RSA cap calculations and considered that this might be appropriate, noting the difficulties identified by the sponsor in agreeing [REDACTED].
- 6.11 The PBAC noted that to facilitate obinutuzumab use with venetoclax, a new obinutuzumab listing would need to be created. In addition, the PBAC noted that minor flow-on changes to the current obinutuzumab CLL restriction for use with chlorambucil would be appropriate to differentiate it from the new venetoclax with obinutuzumab combination listing.
- 6.12 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically the PBAC found that the circumstances of its recommendation for venetoclax:
- a) Treatment with venetoclax is expected to provide a clinically relevant improvement in efficacy over alternative therapies with respect to delaying progression.
 - b) Treatment with venetoclax is not expected to address a high and urgent unmet clinical need because other subsidised therapies are available;
 - c) It was not necessary to make a finding in relation to whether it would be in the

Public Summary Document – July 2020 PBAC Meeting

public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

6.13 The PBAC advised that this submission would not meet the criteria for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

7 Recommended listing

7.1 Add new PBS listings as follows:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
VENETOCLAX venetoclax 10 mg tablet [14] (&) venetoclax 50 mg tablet [7] (&) venetoclax 100 mg tablet [7] (&) venetoclax 100 mg tablet [14], 1 pack	NEW (for RSA monitoring) (Existing: 11630D)	1	1	0	Venclexta

Restriction Summary [new] / Treatment of Concept: [new]

(for internal Dept. use)	Concept ID	Category/Program: GENERAL – General Schedule (Code GE)
		Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
		Restriction type / Method: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment (telephone/online)
		Episodicity: blank
17770	Condition: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)	Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
	Treatment Phase: Initial treatment in first-line therapy – Dose titration (5-week ramp-up schedule)	
New (8594 variation)	Clinical criteria: The condition must be untreated	
	AND	
16058	Clinical criteria:	
16057	Patient must be inappropriate for fludarabine based chemo-immunotherapy	
	AND	
NEW (22681 variation)	Clinical criteria: The treatment must be in combination with obinutuzumab (refer to Product Information for timing of obinutuzumab and venetoclax doses)	
	AND	
16049	Clinical criteria:	
16048	Patient must have a creatinine clearance 30 mL/min or greater	
	AND	
16047	Clinical criteria:	
16046	Patient must have a total cumulative illness rating scale (CIRS) score of greater than 6 (excluding CLL-induced illness or organ damage); or	
10949	Patient must have a creatinine clearance less than 70 mL/min	
25796	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333	
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised	
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised	

Public Summary Document – July 2020 PBAC Meeting

7608	Administrative Advice: 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	Available brands
VENETOCLAX venetoclax 100 mg tablet, 120	NEW	1	120	4	Venclexta

First continuing treatment Restriction Summary [new] / Treatment of Concept: [new]

Concept ID	Category/Program: GENERAL – General Schedule (Code GE)
(for internal Dept. use)	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type / Method: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment (telephone/online)
	Condition: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
17770	Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
	Treatment Phase: First continuing treatment (treatment cycles 2 to 6 inclusive) of first-line therapy
11365	Clinical criteria:
11364	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
(22681 variation)	Clinical criteria:
	The treatment must be in combination with obinutuzumab (refer to Product Information for timing of obinutuzumab and venetoclax doses)
	AND
new	Clinical criteria:
	The treatment must cease upon disease progression
25796	Administrative Advice:
	Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised
7608	Administrative Advice: Special Pricing Arrangements apply

Second/final continuing treatment Restriction Summary [new] / Treatment of Concept: [new]

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
VENETOCLAX venetoclax 100 mg tablet, 120	NEW	1	120	5	Venclexta

Concept ID	Category/Program: GENERAL – General Schedule (Code GE)
(for internal Dept. use)	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type/ Method: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment (telephone/online)
	Condition: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
17770	Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
	Treatment Phase: Second and final continuing treatment prescription (treatment cycles 7 to 12 inclusive) of first-line therapy
11365	Clinical criteria:
11364	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
new	Clinical criteria:
	The treatment must cease upon disease progression; or

Public Summary Document – July 2020 PBAC Meeting

	The treatment must cease upon completion of 12 cycles of treatment with this drug for this condition, whichever comes first
25796	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised
7608	Administrative Advice: Special Pricing Arrangements apply

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
VENETOCLAX					
venetoclax 10 mg tablet, 14	11624T	1	14	0	Venclexta
venetoclax 50 mg tablet, 7	11648C	1	7	0	Venclexta

Edit dose titration Restriction Summary 8676 / Treatment of Concept: 8699

Concept ID	Category/Program: GENERAL – General Schedule (Code GE)
(for internal Dept. use)	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type/ Method: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment (telephone/online)
	Condition: chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
1770	Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
	Treatment phase: Dose modification
8663	Clinical criteria:
8662	The treatment must be for dose titration purposes
insert 25796	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7608	Administrative Advice: Special Pricing Arrangements apply.

7.2 Flow-on changes to the obinutuzumab listing are required to allow use in combination with venetoclax.

Add new obinutuzumab listing as follows:

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	№.of Rpts	Manufacturer
OBINUTUZUMAB Injection	NEW (Public) NEW (Private)	1,000 mg	8	Roche Products Pty Ltd
Available brands				
Gazyva (obinutuzumab 1 g/40 mL injection, 40 mL vial)				

Obinutuzumab in combination with venetoclax treatment Restriction Summary [new] / Treatment of Concept: [new]

Concept ID	Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Private hospitals)
(for internal Dept. use)	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type / Method: <input checked="" type="checkbox"/> Authority Required – Streamlined (new 4 or 5 digit code)

Public Summary Document – July 2020 PBAC Meeting

17770	Indication: Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
	Treatment Phase: For combination use with venetoclax treatment cycles 1 to 6 inclusive in first-line therapy
New (8594 variation)	Clinical criteria: The condition must be untreated
	AND
new	Clinical criteria: The treatment must be in combination with PBS-subsidised venetoclax
11532	Administrative Advice: A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised
7608	Administrative Advice: Special Pricing Arrangements apply

Amend existing CLL listing for obinutuzumab to differentiate it from the above new listing as follows:

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	No. of Rpts	Manufacturer
OBINUTUZUMAB Injection	10407R (Public) 10418H (Private)	1,000 mg	7	Roche Products Pty Ltd
Available brands				
Gazyva (obinutuzumab 1 g/40 mL injection, 40 mL vial)				

Restriction Summary 8207 / ToC: 8184: Authority Required: Streamlined

7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7608	Administrative Advice: Special Pricing Arrangements apply.
Insert	Treatment phase: <i>Combination use with chlorambucil only</i>
10943	Indication: Chronic lymphocytic leukaemia (CLL)
21012	Clinical criteria:
21011	The condition must be CD20 positive
	AND
8594	Clinical criteria:
8593	The condition must be previously untreated
	AND
16058	Clinical criteria:
16057	Patient must be inappropriate for fludarabine based chemo-immunotherapy
	AND
10947	Clinical criteria:
10946	The treatment must be in combination with chlorambucil
	AND
16049	Clinical criteria:
16048	Patient must have a creatinine clearance 30 mL/min or greater
	AND
16047	Clinical criteria:
16046	Patient must have a total cumulative illness rating scale (CIRS) score of greater than 6 (excluding CLL-induced illness or organ damage); or
10949	Patient must have a creatinine clearance less than 70 mL/min
17650	Prescribing Instructions:

Public Summary Document – July 2020 PBAC Meeting

	Treatment must be discontinued in patients who experience disease progression whilst on this treatment.
Edit 16056	Administrative Advice: Obinutuzumab is not to be used as monotherapy or in combination with anti-cancer drugs other than chlorambucil <i>under this restriction. For use with venetoclax, refer to the separate listing for this purpose.</i>
11532	Administrative Advice: A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

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 decision of the PBAC and is working with the Department of Health on the earliest possible PBS listing.