7.03 OBINUTUZUMAB
1000 mg/40 mL solution for infusion, 1 x 40 mL vial; Gazyva®, Roche Products Pty Ltd.

1 Purpose of Application

1.1. The submission sought Section 100 Efficient funding of chemotherapy listing for obinutuzumab in combination with chlorambucil for the treatment of chronic lymphocytic leukaemia (CLL) in unfit elderly patients with comorbidities. The first submission was considered by the PBAC in July 2014.

2 Requested listing

2.1 A summary of the requested listing is outlined below.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
OBINUTUZUMAB solution for intravenous infusion 1,000 mg in 40 mL	1,000 mg	7	Public hospital: Published $[redacted] Effective $[redacted] Private hospital: Published $[redacted] Effective $[redacted]	Gazyva	Roche Products Pty Ltd

Section 100 Efficient funding of chemotherapy
Patient must have CD20 positive chronic lymphocytic leukaemia (CLL), AND
The condition must be previously untreated, AND
The treatment must be in combination with chlorambucil, AND
Patient must have a creatinine clearance 30 mL/min or greater, AND
Patient must have a creatinine clearance less than 70 mL/min; OR
Patient must have a total cumulative illness rating scale (CIRS) score of greater than 6 (excluding CLL-induced illness or organ damage).

2.2 The basis for the requested PBS listing was a cost-utility analysis using two comparators: rituximab plus chlorambucil and chlorambucil monotherapy.

2.3 In comparison with the previous submission, the proposed restriction was amended to be based on the CLL11 trial inclusion and exclusion criteria, as requested by the PBAC in July 2014. Therefore, the proposed restriction included:
- The addition of a criterion of creatinine clearance 30 mL/min or greater, in line with the key trial, which could prevent the use of obinutuzumab in medically frail patients;
- Clarification that the cumulative illness rating scale (CIRS) score criterion excluded illness or organ damage caused by CLL.

2.4 The PBAC recalled the concerns raised by the ESC and DUSC in relation to the July 2014 submission for obinutuzumab, that “there is potential for patients who are

'medically fit' to be considered eligible for obinutuzumab because: the CIRS involves assessments that may be considered to be subjective; assessment of comorbidity other than CLL may be difficult to determine; and many patients would attain a score greater than six including some patients who may be eligible for fludarabine." (Paragraph 2.2, July 2014 Minutes, obinutuzumab). Further, the PBAC had noted that the interpretation of comorbidities in clinical practice may be broader than in the clinical trial, and also that there is potential for retreatment with obinutuzumab, and potential for use after relapse or progression on other treatments.

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

3 Background

3.1 TGA status: registered in May 2014 for the treatment of patients with previously untreated chronic lymphocytic leukaemia.

3.2 The approved TGA indication is broader than the requested PBS restriction because the TGA indication does not restrict use to patients with comorbidities (i.e. a creatinine clearance less than 70 mL/min or a total CIRS score of greater than 6).

3.3 Obinutuzumab in combination with chlorambucil for previously untreated CLL in unfit patients who had comorbidities was considered at the July 2014 PBAC meeting. The PBAC rejected that submission on the basis that it had failed to demonstrate that obinutuzumab was cost-effective. The PBAC had considered that the model was unsuitable as a basis for determining the cost-effectiveness of obinutuzumab.

Table 1: Summary of the previous submission and current re-submission

	Obinutuzumab July 2014	Current re-submission
Requested PBS listing	Patient must have CD20 positive CLL, AND The condition must be previously untreated, AND The treatment must be in combination with chlorambucil, AND Patient must have a total cumulative illness rating scale (CIRS) score of greater than 6; OR Patient must have a creatinine clearance less than 70 mL/min PBAC Comment: listing should be based around trial inclusion and exclusion criteria.	Added: Patient must have a creatinine clearance 30 mL/min or greater Modified: Patient must have a total cumulative illness rating scale (CIRS) score of greater than 6 (excluding CLL-induced illness or organ damage).
Requested price	Effective DPMA Public hospital: $[redacted] Private hospital: $[redacted]	Effective DPMA Public hospital: $[redacted] Private hospital: $[redacted] The requested ex-manufacturer price was unchanged. The ESC noted that the change in the requested DPMA was due to changes to various fees (diluent, preparation, distribution and dispensing fees).

	Obinutuzumab July 2014	Current re-submission
Main comparator	Main comparator: chlorambucil Secondary comparator: rituximab + chlorambucil PBAC Comment: Both chlorambucil and rituximab + chlorambucil appropriate comparators.	Main comparators: - Rituximab + chlorambucil - Chlorambucil Supplementary comparator: - Ofatumumab + chlorambucil
Clinical evidence	CLL11, clinical cut-off 9 May 2013 provided in the submission; 3 March 2014 data cut-off was provided in the PSCR and pre-PBAC response: Stage 1a (vs chlorambucil), N=356 Stage 2 (vs rituximab plus chlorambucil), N=663 PBAC Comment: CLL11 accepted as key trial	CLL11, clinical cut-off 3 March 2014 (provided in PSCR for previous consideration) Stage 1a (vs chlorambucil), N=356 Stage 2 (vs rituximab plus chlorambucil), N=663
Key effectiveness data	Obinutuzumab +chlorambucil vs rituximab +chlorambucil Data from 9 May 2013 data cut-off (per previous submission) PFS, RD (95% CI): –29.1% (–36.3%, –21.8%) OS, HR (95% CI): 0.66 (0.41, 1.06) Obinutuzumab +chlorambucil vs chlorambucil PFS, RD (95% CI): –42.3% (–51.6%, –32.9%) OS, HR (95% CI): 0.41 (0.23, 0.74) PBAC Comment: In comparison with rituximab + chlorambucil, the OS outcome was not statistically significant however approached significance. In July 2014, the PBAC noted that the more recent data (3 March 2014 data –cut) was approaching statistical significance.	Obinutuzumab +chlorambucil vs rituximab +chlorambucil Data from 3 March 2014 data cut-off (also provided in previous PSCR) PFS, RD (95% CI): [redacted] OS, HR (95% CI): 0.70 (0.47, 1.02) Obinutuzumab +chlorambucil vs chlorambucil PFS, RD (95% CI): [redacted] OS, HR (95% CI): 0.47 (0.29, 0.76) Obinutuzumab +chlorambucil vs ofatumumab +chlorambucil PFS, indirect HR (95% CI): 0.32 (0.22, 0.45) TTNT, indirect HR (95% CI): [redacted]
Key safety data	Obinutuzumab +chlorambucil vs rituximab +chlorambucil Serious infusion-related reactions, RD (95% CI): [redacted] Serious neutropenia, RD (95% CI): [redacted] Serious thrombocytopenia, RD (95% CI): [redacted] Obinutuzumab +chlorambucil vs chlorambucil Serious infusion-related reactions, RD (95% CI): [redacted] Serious neutropenia, RD (95% CI): -2.3 (-6.8, 2.3) Serious thrombocytopenia, RD (95% CI): [redacted] PBAC Comment: Inferior safety profile accepted.	Obinutuzumab +chlorambucil vs rituximab +chlorambucil Serious infusion-related reactions, RD (95% CI): [redacted] Serious neutropenia, RD (95% CI): [redacted] Serious thrombocytopenia, RD (95% CI): [redacted] Obinutuzumab +chlorambucil vs chlorambucil Serious infusion-related reactions, RD (95% CI): [redacted] Serious neutropenia, RD (95% CI): [redacted] Serious thrombocytopenia, RD (95% CI): [redacted]
Clinical claim	Superior efficacy and inferior safety compared to chlorambucil Superior efficacy and inferior safety compared to rituximab plus chlorambucil PBAC Comment: Claims accepted.	No change to the claim in relation to the main comparators For the comparison against ofatumumab: The PSCR claimed a statistically significant improvement in PFS (HR=0.32, 95% CI:0.22, 0.45) and time to next anti-leukaemia treatment (HR=[redacted], 95% CI: [redacted]), and similar safety compared to ofatumumab plus chlorambucil.

	Obinutuzumab July 2014	Current re-submission
Economic evaluation	Cost-utility model with incremental cost/QALY Model structure: Progression-free survival (on treatment, off treatment); Progressive disease; Death; Overall survival: based on CLL11 and CLL5; Parametric extrapolation: Gompertz and gamma (Stage 1a); Gompertz and log-logistic (Stage 2); Costs: drug acquisition, premedications, IV administration, medical resource use, selected serious adverse events PBAC Comment: ICERs not accepted because the economic model was deemed inappropriate in terms of structure, inputs and outcomes	Cost-utility model with incremental cost/QALY Model structure: Progression-free survival (on treatment, off treatment); Asymptomatic progression; Symptomatic progression (on treatment, off treatment, subsequent progression); Death; Overall survival: based on CLL11; Parametric extrapolation: Weibull (Stage 1a); Gamma (Stage 2); Costs: ADDED post-progression medical resource use, additional lines of treatment, end of life, adverse events related to secondary malignancies and cardiac events
ICER	$ versus rituximab plus chlorambucil; $ versus chlorambucil.	$ versus rituximab plus chlorambucil; $ versus chlorambucil.
Number of patients	• in Year 1 increasing to in Year 5. PBAC Comment: difficult to reliably estimate the number of patients who are likely to use obinutuzumab	• in Year 1 increasing to in Year 5.
Estimated cost to PBS	•$ in Year 1 increasing to $ in Year 5 for a total of $ over the first 5 years of listing (at effective price after rebate). PBAC Comment: actual cost may be higher or lower due to uncertain estimate of patient numbers and the risk of use outside the restriction	•$ in Year 1 increasing to $ in Year 5 for a total of $ over the first 5 years of listing (at effective price after rebate) (values recalculated during evaluation)
PBAC decision	•Reject Item 7.23. Evaluation of a revised economic model structure with appropriate inputs would require a major re submission.	-

Source: Compiled during the evaluation
RD = risk difference; HR = hazard ratio; PFS = Progression-free survival; OS = Overall survival; PSCR = Pre-Sub Committee Response; TTNT = Time to next treatment; IV = intravenous; DPMA = Dispensed Price for Maximum Amount.

3.4 In November 2014, the PBAC recommended ofatumumab for the treatment of CLL in previously untreated patients who are unable to have fludarabine-based therapy. Listing was recommended on the basis of a cost-minimisation analysis compared to rituximab. The PBAC considered that, based on an indirect comparison using chlorambucil as the common comparator, ofatumumab + chlorambucil was unlikely to be superior to rituximab + chlorambucil in the treatment of previously untreated patients with CLL. The PBAC considered both ofatumumab and rituximab significantly prolong PFS when combined with chlorambucil in first line treatment of CLL, and both have an acceptable toxicity profile when combined with chlorambucil in patients unsuitable for fludarabine-based therapy.

3.5 On 1 December 2014, rituximab was listed for the treatment of CLL in combination with chemotherapy. Prior to this, rituximab was only listed for use in CLL in combination with fludarabine and cyclophosphamide.

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

4 Clinical place for the proposed therapy

4.1 The clinical place for the proposed therapy was unchanged from the previous submission. Obinutuzumab is to be used in combination with chlorambucil. It was proposed as a first-line treatment for previously untreated, unfit patients with CD20 positive CLL and comorbidities. The patients are likely to be elderly. The comorbidities were defined as a total CIRS score of more than six, creatinine clearance (CrCl) <70 mL/min, or both. Further, in the re-submission's updated restriction, patients were also required to have a creatinine clearance 30 mL/min or greater, and the restriction specified that the CIRS score excludes CLL-induced illness or organ damage.

4.2 The ESC considered that the treatment algorithm for CLL is rapidly evolving, and noted that the place in therapy proposed for obinutuzumab was similar to that requested for ofatumumab: that is, for use in previously untreated patients who are unfit/inappropriate for fludarabine based therapy.

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

5 Comparator

5.1 The submission nominated two main comparators:
- Rituximab plus chlorambucil,
- Chlorambucil monotherapy.

Both comparators were accepted by the PBAC in July 2014. The submission stated that obinutuzumab plus chlorambucil was expected to replace the nominated comparators in the first-line treatment of patients with CLL who were elderly and/or had comorbidities.

5.2 The submission considered ofatumumab plus chlorambucil as a supportive comparator and provided comparative clinical efficacy and safety data.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (6) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with obinutuzumab, including that it allows people to be in remission for longer, improves quality of life, provides hope, reduces fear and anxiety, and 'as treatment naive, the benefits will be when treatment is needed'.

6.3 Representatives of the PBAC met with Lymphoma Australia prior to the PBAC meeting, and reported the following key points to the PBAC in relation to the agenda items for CLL and indolent NHL:

- Consumers place high importance on having access to the best available treatments. Where cure is not possible, the eventual goal would be to enable indolent lymphomas and CLL to be treated as chronic diseases. Ultimately patients may die of conditions unrelated to their lymphoma.

- Patients may relapse multiple times in the course of the disease, and will be treated on relapse. As PBS subsidy may influence the choice of treatment, subsidising the most clinically effective treatments is critical to ensure the best value for the taxpayer.

- Patients may be diagnosed at a young age and live for years after diagnosis, and therefore place a high value on PFS. Patients who are well during the progression free period can resume day-to day functions including participating in the workforce and family life. In this context, the decision for the patient rests on a balance of the PFS gained against the quality of life impacts of drug toxicity. The psychological impact of patients' fear of relapse can have a highly detrimental effect on their quality of life.

The PBAC noted and welcomed this input. The PBAC recognises that a drug may be useful even when it does not provide a survival advantage, but does provide quality of life benefits. In terms of using PFS to value the benefits of a drug, PBAC recalled that some of the most informative submissions seen to date have presented economic models that incorporate the impacts on quality of life when patients are in a PFS state, capturing the fact that PFS is not an homogenous state. It was noted that exploring how patients could provide more input to rigorous measurement of Quality of Life would be valuable in future consumer submissions.

Clinical trials

6.4 The re-submission was based on one open-label head-to-head trial (CLL11) comparing obinutuzumab plus chlorambucil with rituximab plus chlorambucil in Stage 2 of the trial and with chlorambucil monotherapy in Stage 1a. The key trial was the same as in the previous submission. The most recent data-cut for this trial (3 March 2014) had been provided in the Pre-Sub-Committee Response (PSCR) and pre-PBAC response for the previous submission.

6.5 Details of the trial presented in the re-submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID/ First Author	Protocol title/ Publication title	Publication citation
Direct randomised trial (main comparators)		
CLL11	Primary Clinical Study Report - BO21004/CLL11 - Stage 1a (GClb vs. Clb) – An open-label, multi-centre, three arm randomized, phase III study to compare the efficacy and safety of RO5072759 + chlorambucil (GClb), rituximab + chlorambucil (RClb) or chlorambucil (Clb) alone in previously untreated CLL patients with comorbidities. Research Report Number 1038127.	March 2013
	Update Clinical Study Report – BO21004: Stage 1a – 1b Update. Research Report Number 1057363.	December 2013
	Primary Clinical Study Report − BO21004/CLL11 − Stage 2 (GClb vs. RClb) – Research Report Number 1056550.	December 2013
	Update Clinical Study Report – BO21004: Stage 2 – 1a Update. Report Number 1060313.	June 2014
Goede	Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions.	N Eng J Med 2014 370 (12):1101-10
Direct randomised trial (for indirect comparison)		
COMPLEMENT-1	ClinicalTrials.gov Identifier NCT00748189.	2014
	Study OMB110911. Results summary for COMPLEMENT-1. GSK Clinical Trials Register.	November 2013
	European Medicines Agency. CHMP assessment report for Arzerra. Report number EMA/475698/2014.	May 2014

Source: Table B.2.2 pp.4-5 of the commentary.

6.6 The key features of the randomised trials 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
Obinutuzumab +chlorambucil vs rituximab plus chlorambucil						
CLL11 Stage 2	663	R, OL, MC Median 6 mths	Unclear	Previously untreated CLL with comorbidities	PFS, OS, TTNT	Yes
Obinutuzumab +chlorambucil vs chlorambucil						
CLL11 Stage 1a	356	R, OL, MC Median 6 mths	Unclear	Previously untreated CLL with comorbidities	PFS, OS, TTNT	Yes
Obinutuzumab +chlorambucil vs ofatumumab + chlorambucil (indirect)						
COMPLEMENT-1	447	R, OL, MC median 159 days	Low	Previously untreated CLL and inappropriate for fludarabine-based therapy	PFS, OS, TTNT	No

Source: compiled during the evaluation.
R = randomised; MC = multi-centre; OL = open label; OS = overall survival; PFS = progression-free survival; TTNT = time to next treatment; CLL = chronic lymphocytic leukaemia; mths = months

6.7 Progression-free survival (PFS) was the primary outcome in the CLL11 trial. Overall survival (OS) and time to next anti-leukaemia treatment were secondary outcomes.

6.8 The PBAC noted that the CLL11 trial was open-label and the primary outcome was investigator-assessed PFS.

Comparative effectiveness

6.9 The results for the comparison with chlorambucil are presented in Table 1, and not further reported below. The results for the comparison with rituximab plus chlorambucil are presented in Table 4.

6.10 Relative to both main comparators, obinutuzumab plus chlorambucil resulted in significantly longer times to progression and times to next anti-leukaemia treatment. In comparison with rituximab plus chlorambucil, the hazard ratio for PFS was 0.40 (95% CI: 0.33 to 0.50) and the hazard ratio for time to next treatment was 0.54 (95% CI: 0.40 to 0.72). In July 2014, the PBAC considered that obinutuzumab was superior to rituximab (both in combination with chlorambucil) in terms of comparative effectiveness in relation to PFS. In July 2014, the PBAC noted that while the hazard ratio for OS was not statistically significant, the point estimate was in favour of obinutuzumab and approaching statistical significance (HR 0.70, 95% CI: 0.47 to 1.02) (paragraph 7.10, Ratified Minutes, July 2014).

6.11 The results for the indirect comparison with ofatumumab are presented in Table 5. The submission considered that obinutuzumab was superior to ofatumumab (both in combination with chlorambucil). Due to differences between the chlorambucil arms of the two trials, the statistically significant differences for PFS and time to next anti-leukaemia treatment should be interpreted with caution.

6.12 The PSCR stated that it can be inferred that obinutuzumab is likely to be superior to ofatumumab (both in combination with chlorambucil) in relation to PFS because the PBAC has previously accepted that:

- ofatumumab is non-inferior to rituximab (citing the 'Recommendations made by PBAC – November 2014').
- obinutuzumab is superior to rituximab in terms of comparative effectiveness in relation to PFS (Paragraph 7.10, PBAC Minutes July 2014).

6.13 However, the ESC considered that the submission had not demonstrated superior effectiveness of obinutuzumab compared to ofatumumab (both in combination with chlorambucil). The ESC agreed with the evaluation that the indirect comparison may not have been reliable due to differences in baseline characteristics and differing chlorambucil doses. Outcomes in the common reference arms did not seem comparable between CLL11 and COMPLEMENT-1, and some of these differences may have resulted from patient cross over in the CLL11 trial. In particular, the 'time to next treatment' in the common reference arm (chlorambucil monotherapy) was [redacted] months in one trial and 24.7 months in the other. The ESC considered that this difference may have led to the statistically significant hazard ratio favouring obinutuzumab for this outcome.

6.14 The submission did not present OS results in the indirect comparison against ofatumumab because OS results for ofatumumab had not been published.

Comparative harms

6.15 For the comparisons against chlorambucil and chlorambucil+rituximab, the CLL11 trial data showed the obinutuzumab arm had an inferior safety profile relative to its comparators. The most common treatment-related Grade 3 to 5 (moderate to severe) adverse events were infusion-related reaction, neutropenia, and thrombocytopenia.

6.16 For the comparison against ofatumumab, an indirect comparison of safety outcomes suggested that obinutuzumab plus chlorambucil was more likely to result in adverse events leading to dose modification or interruption and in treatment-related adverse events. This was despite the fact that the ofatumumab intervention used a higher dose of chlorambucil.

Benefits/harms

6.17 A summary of the comparative benefits and harms for obinutuzumab plus chlorambucil versus and rituximab plus chlorambucil is presented in the table below.

Table 4: Summary of comparative benefits and harms for obinutuzumab plus chlorambucil and rituximab plus chlorambucil at median follow-up of 27.3 months

Benefits				
	Obinutuzumab +chlorambucil	Rituximab +chlorambucil	RD (95% CI)	HR (95% CI)
Progression free survival				
Progressed	[redacted]	[redacted]		0.40 (0.33, 0.50)
median PFS (mths)	29.2 [redacted]	15.4 [redacted]	[redacted]	
Overall survival				
died	45/333 (13.5%)	63/330 (19.1%)		0.70 (0.47, 1.02)
median OS (mths)	– ([redacted], –)	– (–,–)	NC	
Time to new treatment				
events	[redacted]	[redacted]		0.54 (0.40, 0.72)
median TTNT (mths)	42.7 (39.6, −)	32.7 (27.8, −)	[redacted]	

Harms						
	Obinutuzumab +chlorambucil	Rituximab +chlorambucil	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				Obinutuzumab +chlorambucil	Rituximab +chlorambucil	
Infusion-related reactions (Grade 3-5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia (Grade 4)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia (Grade 3-4)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All grade infections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table B.6.3 p.37, Table B.6.5 p.41, Table B.6.7 p.43, Table B.6.20 p.61 and Table B.6.22 p.64 of the submission.
[a]No Grade 5 adverse events were recorded for neutoprenia and thrombocytopenia.
Abbreviations: RD = risk difference; HR = hazard ratio; CI = confidence interval; OS = overall survival; TTNT = time to next treatment; mths = months; NC = not calculated.

6.18 On the basis of direct evidence presented by the re-submission, the comparison of obinutuzumab plus chlorambucil and rituximab plus chlorambucil over a median follow-up of 27.3 months, resulted in:

- An improvement in median PFS of approximately 13.8 months,
- Approximately 29 fewer patients per 100 having progressed,
- Approximately 13 fewer patients per 100 patients requiring a re-treatment,
- No differences in overall survival.

On the basis of direct evidence presented by the re-submission, for every 100 patients treated with obinutuzumab plus chlorambucil, in comparison to rituximab plus chlorambucil, over a median duration of follow-up of 27.3 months

- Approximately 16 additional patients would have Grade 3-5 infusion-related reactions,
- Approximately 7 additional episodes of grade 4 neutropenia but no additional episodes of infection (all-Grade infection)
- Approximately 7 additional patients would have Grade 3- 4 thrombocytopenia.

6.19 A summary of the comparative benefits and harms for obinutuzumab plus chlorambucil versus and ofatumumab plus chlorambucil is presented in the table below.

Table 5: Summary of benefits and harms for obinutuzumab plus chlorambucil and ofatumumab plus chlorambucil based on an indirect comparison

Benefits					
	OBI +CLB	CLB	OFA + CLB	Absolute Difference	HR (95% CI)
Progression free survival					
Progressed					
CLL-11	[redacted]	[redacted]		-	0.18 (0.14, 0.24)
COMPLEMENT-1		151/226	136/221		0.57 (0.45, 0.72)
Indirect comparison					0.32 (0.22, 0.45)
Median PFS (mths)					
CLL-11	29.9 [redacted]	11.1 [redacted]		18.8	
COMPLEMENT-1		13.1 (10.6, 13.8)	22.4 (19.0, 25.2)	9.3	
Time to next treatment					
Events					
CLL-11	[redacted]	[redacted]			[redacted]
COMPLEMENT-1		99/226	64/221		0.49 (0.36, 0.67)
Indirect comparison					[redacted]
Median TTNT (mths)					
CLL-11	[redacted]	[redacted]		[redacted]	
COMPLEMENT-1		24.7 (22.6, 29.1)	39.8 (34.7, 48.8)	15.1	

Harms								
	OBI +CLB	CLB	OFA +CLB	RR (95% CI)	Event rate/100 patients			RD (95% CI)
					OBI +CLB	CLB	OFA + CLB	
Any AE								
CLL-11	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]
COMPLEMENT-1		203/227	206/217	1.1 (1.0, 1.1)		89	95	5.5 (0.6, 10.5)
Indirect comparison				[redacted]				[redacted]
Severe AEs								
CLL-11	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]
COMPLEMENT-1		103/227	131/217	1.3 (1.1, 1.6)		45	60	15.0 (5.8, 24.2)
Indirect comparison				[redacted]				[redacted]
Deaths								
CLL-11	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]
COMPLEMENT-1		40/227	34/217	0.9 (0.6, 1.4)		18	16	-2.0 *(-8.9, 5.0)*
Indirect comparison				[redacted]				[redacted]

Source: Table B(a).6.1 p.28 of the submission. HR = hazard ratio; CI = confidence interval; OBI = obinutuzumab; CLB = chlorambucil; OFA = ofatumumab; AE = adverse event.

6.20 Based on an indirect comparison using chlorambucil as the common comparator, the comparison of obinutuzumab and ofatumumab resulted in a statistically significant difference in PFS and time to next treatment. The ESC considered that this indirect evidence may not have been reliable, as outlined in Paragraph 6.13.

Clinical claim

6.21 The re-submission claimed that obinutuzumab plus chlorambucil was superior in terms of effectiveness, and was inferior in terms of safety, when compared to:
- rituximab plus chlorambucil,
- chlorambucil monotherapy.

The claim was unchanged from the previous submission. This claim had been accepted by the PBAC in July 2014.

6.22 The submission also claimed that obinutuzumab plus chlorambucil resulted in a statistically significant improvement in PFS (HR=0.32, 95% CI:0.22, 0.45) and time to next anti-leukaemia treatment (HR=[redacted], 95% CI: [redacted]), and similar safety compared to ofatumumab plus chlorambucil.

6.23 This claim against ofatumumab was potentially inadequately supported due to:
- Differences between trials in baseline characteristics (age, comorbidity) and chlorambucil dosage (considerably higher in COMPLEMENT-1);
- Differences in the clinical outcomes in the reference arms of the two trials were substantial, which made the analysis questionable;
- Evidence of effectiveness in terms of overall survival was not available.

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

Economic analysis

6.24 The re-submission presented a modelled evaluation for the comparisons with rituximab plus chlorambucil, and chlorambucil monotherapy. The re-submission did not provide an economic evaluation comparing obinutuzumab plus chlorambucil with ofatumumab plus chlorambucil.

6.25 In July 2014, the PBAC had raised a number of concerns about the economic evaluation submitted for obinutuzumab versus rituximab+chlorambucil, and chlorambucil monotherapy. Table 6 outlines the changes that were made to the model to address each of these concerns.

Table 6: Economic evaluation: Matters raised by the PBAC in July 2014 and how these were addressed in the re-submission

Issues identified with the model submitted in July 2014	How the issue was addressed in the re-submission
The method used to derive the probability of post-progression survival, using data from the CLL5 trial, led to inconsistency between the modelled and observed OS (Para 7.12 of July 2014 Minutes). The PBAC suggested that an appropriate model should ensure modelled OS is consistent with the trial-based data (Para 7.17)	CLL11 data were relied on for the modelling of post-progression survival probabilities.
The structure of the economic model did not appropriately reflect different levels of disease progression, and required an additional health state to account for patients who are progressed but well. (Para 7.13) The PBAC suggested that an appropriate model should include a progressed but well health state with an appropriate utility value.	The model structure was modified to more appropriately reflect the paths of disease progression. The health state of 'post-progression' were replaced with: - Asymptomatic progression - Symptomatic progression (on treatment, without treatment) - Subsequent progression Additional utility weights were used from Kosmas et al (2014) for the health states that had been added in the model.
The model must include the impact of post progression therapy, given the likelihood that patients with progressive disease may receive second and subsequent lines of treatment; a reliable model structure would need to appropriately reflect the possibility of additional lines of treatment, with their costs and health benefits. (Para 7.14) The PBAC suggested that an appropriate model should include post-progression therapy in the base case, with this excluded in a sensitivity analysis;	The cost of an additional line of treatment was assumed to be equal to [redacted] cycles of rituximab plus chlorambucil. Only one additional line of treatment was accounted for in the model. The effectiveness of additional lines of treatment was not explicitly modelled. The re-submission argued the health benefits were inherently reflected by the CLL11 data used to model post-progression probabilities. The impact on health state utilities was supposed to be incorporated in the relevant weights used in the model. The evaluation considered that this was probably reasonable. Sensitivity analyses were undertaken by doubling the cost of second-line treatment, and also by assuming zero weeks on second-line therapy.
The model was highly sensitive to the choice of parametric function used to extrapolate PFS when the more recent data cut is used; moreover, the model was highly sensitive to the choice of data cut. (Para 7.15)	The outcomes of economic evaluation were still somewhat sensitive to the choice of the parametric form for data extrapolation. Relevant sensitivity analyses were presented.
The costs of adverse events should be included in the model (para 7.17)	The costs of adverse events were accounted for in a more comprehensive manner and included infusion-related reactions, neutropenia, thrombocytopenia, secondary malignancies, and cardiac events.

Source: compiled during evaluation

CIRS = cumulative illness rating scale; CLL = chronic lymphocytic leukaemia; PBAC = Pharmaceutical Benefits Advisory Committee; PFS = progression free survival; PSCR =pre sub-committee report

6.26 Key changes made to the model to address the PBAC's concerns from July 2014 included:

- the inclusion of additional health states, i.e. the progressed state subdivided into asymptomatic, symptomatic on treatment, symptomatic off treatment, and subsequent progression;
- the use of more recent data for the modelling of overall survival (CLL11 rather than CLL5);
- the inclusion of additional cost categories i.e. end of life, adverse events, medical resource use in post-progression, additional line of treatment.

The evaluator and the ESC considered that these changes were appropriate.

Table 7: Summary of model structure and rationale

Component	Summary
Time horizon	10 years extrapolated from CLL11 median follow ups of 31.8 months (CLL11 Stage 1a) and 27.3 months (CLL11 Stage 2)
Outcomes	Mean QALYs, mean LYs, total cost
Methods used to generate results	Markov model, cohort expected value analysis, extrapolated trial data
Health states	Progression-free survival (on treatment or without treatment) Asymptomatic progression Symptomatic progression (on treatment or without treatment) Subsequent progression Death
Cycle length	1 week with half-cycle correction
Transition probabilities	Derived from CLL11

Source: compiled during the evaluation. LY = life year; QALY = quality adjusted life year

6.27 The main influences on the ICER identified in the stepped analyses were: extending the model beyond the trial duration; and the inclusion of an additional line of therapy after disease progression. The price of rituximab applied in the economic evaluation was the effective non-fludarabine + cyclophosphamide ex-manufacturer price in CLL as listed on 1 December 2014.

Table 8: Key drivers of the model

Description	Method/Value	Impact
Time horizon	10 years extrapolated from 31.8 or 27.3 months	High, favours obinutuzumab
Extrapolation beyond trial duration	The choice of parametric function based on a visual inspection of Kaplan-Meier curves rather than on Akaike Information Criterion	Moderate, favours comparators
Inclusion of costs of an additional line of treatment	[redacted] cycles of rituximab plus chlorambucil therapy applied in symptomatic post-progression	Moderate, favours obinutuzumab

Source: compiled during the evaluation.

6.28 The submission used a stepped evaluation to calculate the incremental cost per quality-adjusted life year (QALY) gained and incremental cost per life year gained.

Table 9: Results of the stepped economic evaluation

Step and component	Stage 2			Stage 1a		
	OBI + CLB	RIT + CLB	**Δ outcome**	OBI + CLB	CLB	**Δ outcome**
Step 1: trial based costs and outcomes						
Cost	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$272	$ [redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	$ [redacted]			$ [redacted]		
Step 2: parametric extrapolation from median follow ups of 27.3 and 31.8 months to 10 years						
Cost	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$272	$ [redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	$ [redacted]			$ [redacted]		
Base case						
Cost	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$19,270	$ [redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	$ [redacted]			$ [redacted]		
PREVIOUS SUBMISSION						
Cost	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$1,252	$ [redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	$ [redacted]			$ [redacted]		

Source: Tables D.5.1 to D.5.7 pp.31-35 of the submission.
QALY = quality-adjusted life year; Incr. = incremental; OBI = obinutuzumab; CLB = chlorambucil; RIT = rituximab

6.29 The economic evaluation resulted in an incremental cost per QALY gained of $15,000/QALY - $45,000/QALY (versus rituximab plus chlorambucil) and $15,000/QALY - $45,000/QALY (versus chlorambucil). The ICERs reported in the previous submission were $45,000/QALY – $75,000/QALY and $45,000/QALY – $75,000/QALY, respectively. Compared to the previous submission, the re-submission's economic evaluation resulted in an improvement in the cost-effectiveness of obinutuzumab. The ESC noted that this was driven by an increase in the incremental effectiveness, rather than a difference in the costs.

6.30 With respect to other changes suggested by the PBAC in July 2014:

- Effectiveness of additional lines of treatment was not explicitly modelled. However the impact of additional lines of treatment on efficacy outcomes was inherently captured by post-progression survival and overall survival in the CLL11 trial. These outcomes reflected the impact of additional lines of treatment that patients received in this trial (e.g. [redacted]% of patients initially treated with obinutuzumab went on to receive rituximab-based treatment in a later line of therapy). Therefore, the evaluator and the ESC considered that the revised model had appropriately accounted for the effectiveness of additional lines of treatment.
- Only one line of additional treatment was accounted for after progression. The ESC agreed with the evaluation that this approach was conservative as adding further lines would have favoured obinutuzumab. The PSCR argued that this means that the ICER presented represents "ceiling results".

6.31 The submission extrapolated PFS beyond median follow-up using the "best fitting" parametric model. This was determined based on the best visual inspection of fit, rather than the best statistical fit using the Akaike Information Criterion. However, this choice can be considered conservative because it did not favour obinutuzumab. Therefore, the PBAC did not consider this to be a concern in this instance.

6.32 Overall the ESC considered that the updated economic evaluation was more reliable than the model presented in July 2014, and that it addressed the main issues raised by the PBAC in July 2014.

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

Drug cost/patient per average course: $[redacted]

6.33 This is based on an average of [redacted] scripts per patient.

6.34 A complete obinutuzumab treatment comprises six cycles of 28 days. Obinutuzumab is administered three times within the first cycle and once in each of the remaining six cycles (maximum of eight doses in total).

Estimated PBS usage & financial implications

6.35 This re-submission was not considered by DUSC. The estimation of financial impacts used both incidence data and market share data. The key sources included AIHW, PBS, IPSOS market research, the key trial, and Advisory Board advice.

Table 10: Estimated use and financial implications

	2015	2016	2017	2018	2019
Estimated extent of use					
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share [a]	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Scripts [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost [c]					
to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
to State and Territory health budget services	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated total net cost					
Re-submission	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Previous submission					
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated total net cost	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Compiled during the evaluation. *An error in calculation of cost offsets was corrected during the evaluation and accepted in the PSCR. Italics = revised during ESC advice to account for small difference in rounding.*

a – assumed uptake: [redacted]% from chlorambucil monotherapy, rituximab plus chlorambucil, and other rituximab regimens, [redacted]% from FCR-lite, [redacted]% from other chemotherapy;

b – average [redacted] scripts per patient;

c – including [redacted]% price rebate

6.36 The estimated extent of use was less than 10,000 patients treated per year. The estimated total net cost in the resubmission was $10 - $20 million per year.

6.37 The estimated script numbers did not account for the possibility of market growth or leakage outside the proposed restriction, therefore the actual financial impacts could be higher than projected. Other assumptions used to estimate patient numbers (e.g. uptake rate or delay in the 'watch and wait' treatment strategy) were also non-conservative and therefore the cost of listing obinutuzumab may be considerably higher than estimated in the submission. Further, the listing of rituximab in combination with chemotherapy in CLL from 1 December 2014 could affect the market share of CLL drugs, thus limiting the reliability of the estimates.

Quality Use of Medicines

6.38 As in the previous submission, the re-submission discussed the Risk Management Plan approved by the TGA, as well as the potential for off-label use.

Financial Management – Risk Sharing Arrangements

6.39 The re-submission proposed subsidisation caps that if reached, would trigger a price rebate and would reduce the price of obinutuzumab [redacted]. The caps were increased from the previous submission. The re-submission maintained the proposed [redacted]% rebate on the ex-manufacturer price to the Government.

6.40 The PBAC recalled that in its July 2014 consideration of obinutuzumab, it had considered that it was

> 'difficult to reliably estimate the number of patients who are likely to use obinutuzumab. In particular the PBAC considered that there was a risk of use of the drug outside the intended restriction, and agreed with the DUSC that there is potential for retreatment with obinutuzumab, and potential for use after relapse or progression on other treatments'.
>
> 'Further, in light of the uncertain patient numbers and the risk of use of obinutuzumab outside the requested restriction, the PBAC pre-empted that a risk-sharing arrangement would be required should obinutuzumab be recommended for listing in the future. The PBAC considered that [redacted]
>
> (Paragraphs 7.19 and 7.21, July 2014 Minutes, obinutuzumab).

6.41 The PBAC considered, among other matters, that its assessment that the cost-effectiveness of obinutuzumab would be acceptable if the measures below were implemented to manage any unexpected financial impact given the uncertain patient numbers:

- A Risk Sharing Arrangement (RSA) between the sponsor and the Government;
- The RSA should include a [redacted]

[redacted]

7 PBAC Outcome

7.1 The PBAC recommended the listing of obinutuzumab on the PBS for the treatment of CLL in patients with comorbidities on the basis that it should be available only under special arrangements under Section 100. The PBAC considered that a written authority listing would be appropriate for obinutuzumab to help prevent usage beyond the population in whom the comparative effectiveness and cost-effectiveness of the drug have been demonstrated, particularly given the restriction's use of a potentially subjective rating scale (CIRS).

7.2 The PBAC was satisfied that obinutuzumab in combination with chlorambucil provides, for some patients, a significant improvement in efficacy over rituximab plus chlorambucil, and chlorambucil monotherapy.

7.3 The PBAC welcomed and noted the input received from individuals and organisations in support of the submission for obinutuzumab. The comments highlighted that obinutuzumab prolongs remission, provides hope and reduces the fear and anxiety of relapse.

7.4 The PBAC considered that the place in therapy proposed for obinutuzumab was appropriate, noting that the submission pertained to previously untreated patients requiring therapy who are unsuitable for fludarabine-based chemo-immunotherapy, where specific criteria are met, including either a creatinine clearance of less than 70mL/min or a CIRS score of greater than 6 (excluding CLL-induced illness of organ damage).

7.5 The PBAC considered that there is a high risk of usage of obinutuzumab outside the restriction and that this risk remains high, even with a PBS-listed alternative/s for patients with CLL who cannot tolerate fludarabine-based regimens. In forming this view the PBAC noted the concerns raised in Paragraph 2.4, and particularly noted that there is potential for patients who are 'medically fit' to be considered eligible for obinutuzumab because the CIRS involves assessments that may be subjective. Further, the CIRS has not been used in a PBS restriction before.

7.6 The PBAC advised that the restriction level could be reviewed after the initial two years of listing, with a view to changing it to a streamlined authority listing if appropriate.

7.7 With regard to the comparative efficacy and safety of obinutuzumab, the PBAC reiterated its advice from July 2014:

- "The PBAC accepted the submission's claim that obinutuzumab plus chlorambucil is superior in terms of comparative effectiveness and inferior in terms of comparative safety over chlorambucil alone."
- "With regard to the comparison against rituximab plus chlorambucil, the PBAC accepted the submission's claim that obinutuzumab plus chlorambucil is superior in terms of comparative effectiveness in relation to PFS, and inferior in terms of comparative safety. The PBAC noted that while the hazard

ratio for OS was not statistically significant, the point estimate was in favour of obinutuzumab plus chlorambucil and the more recent data is approaching statistical significance (HR: 0.70 [0.47,1.02]).” [Paragraphs 7.9 and 7.10, July 2014 PBAC Minutes, obinutuzumab]

7.8 For the comparison against ofatumumab plus chlorambucil, the PBAC agreed with the ESC that the indirect comparison may not be reliable due to differences in baseline characteristics of patients in the trials. The PBAC recalled that in November 2014 it had not accepted that ofatumumab was superior to rituximab when each was combined with chlorambucil. Therefore, the PBAC considered that the direct comparison of obinutuzumab with rituximab when each were combined with chlorambucil was the critical data upon which to make a decision for PBS subsidy of obinutuzumab.

7.9 The PBAC considered that the amendments made to the economic evaluation addressed the main issues raised in its previous consideration of obinutuzumab, as outlined in Paragraphs 6.25, 6.26 and 6.30.

7.10 In particular, the PBAC noted that the revised model structure more appropriately reflected the course of the condition including the levels of patient health during disease progression. This was because the re-submission subdivided the ‘progressive disease’ health state into four states: asymptomatic progression; symptomatic progression while on treatment; symptomatic progression without treatment and subsequent progression. The ‘asymptomatic progression’ health state accounted for patients who are progressed but well (i.e. patients who have progressed but do not need therapy for CLL). The PBAC recalled that, in July 2014, it had considered that such a health state was necessary given the length of time patients in the CLL11 trial spent between progressing and requiring their next anti-leukemia therapy, and also given the considerable difference in utility weights between the “progression-free survival without treatment” and “progressive disease” health states that were used in the July 2014 model, which had utility weights of 0.82 and 0.66, respectively.

7.11 The PBAC therefore considered that the model was a suitable basis for determining the cost-effectiveness of obinutuzumab in the requested treatment setting. The PBAC considered that the resulting ICERs of $15,000/QALY - $45,000/QALY and $15,000/QALY - $45,000/QALY for the comparisons against rituximab plus chlorambucil, and chlorambucil monotherapy respectively, were reliable.

7.12 The PBAC considered that it is difficult to reliably estimate the number of patients who are likely to use obinutuzumab. The PBAC recalled that in July 2014 it had noted the high risk of usage outside the intended restriction, and that the financial estimates relied on clinical opinion and market research. The PBAC considered that the use of a written authority for the first two years of listing would enable a more accurate estimation of the patient population.

7.13 The PBAC advised that obinutuzumab is not suitable for prescribing by nurse practitioners.

7.14 The PBAC recommended that the Safety Net 20 Day Rule should not apply.

7.15 The PBAC noted that this submission is not eligible for an Independent Review because a positive recommendation was made.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
OBINUTUZUMAB solution for intravenous infusion 1,000 mg in 40 mL	1,000 mg	7	Gazyva	Roche Products Pty Ltd

Category / Program	Section 100 (efficient funding of chemotherapy arrangements) public/private hospital (Written Authority Required)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity:	Previously untreated
Condition:	CD20 positive Chronic Lymphocytic Leukaemia
Indication:	Previously untreated CD20 positive Chronic Lymphocytic Leukaemia
Treatment phase:	Initial and continuing treatment
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	Patient must require treatment for CD20 positive Chronic Lymphocytic Leukaemia AND The condition must be previously untreated AND Patient must be inappropriate for fludarabine based chemo-immunotherapy AND The treatment must be in combination with chlorambucil AND Patient must have a creatinine clearance 30 mL/min or greater AND Patient must have a creatinine clearance less than 70 mL/min; OR Patient must have a total cumulative illness rating scale (CIRS) score of greater than 6 (excluding CLL-induced illness or organ damage).

Prescriber Instructions	Treatment must be discontinued in patients who experience disease progression while on treatment Applications for authorisation must be in writing and must include: (a) a completed authority prescription form; AND (b) documentation that the patient has CD20 positive CLL (flow cytometry pathology report from blood or bone marrow, noting that this may be from some time earlier); AND (c) a statement that the patient is previously untreated, is inappropriate for fludarabine based chemo-immunotherapy, that treatment will be in combination with chlorambucil, (d) documentation that the patient has a creatinine clearance 30 mL/min or greater; AND (e) One of the following, either: - A completed cumulative illness rating scale (CIRS) score form demonstrating that the patient has a score of greater than 6 (excluding CLL-induced illness or organ damage) OR - Documentation that the patient has a creatinine clearance less than 70 mL/min;
Administrative advice	Note Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Written applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001 Note Obinutuzumab is not to be used as monotherapy or in combination with anti-cancer drugs other than chlorambucil Note A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime. Note No increase in the maximum quantity or number of units may be authorised Note No increase in the maximum number of repeats may be authorised Note Special pricing arrangements apply

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The PBAC's decision to recommend obinutuzumab for PBS listing is welcome news for patients and their families.