

## 5.10 OBINUTUZUMAB, solution for IV infusion, 1000 mg/40 mL, Gazyva<sup>®</sup>, Roche Products Pty Ltd.

### 1 Purpose of Application

- 1.1 To seek a Section 100 Efficient Funding of Chemotherapy listing for obinutuzumab in combination with chlorambucil for the treatment of chronic lymphocytic leukaemia (CLL) in patients with comorbidities.

### 2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. 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

#### **Section 100 Efficient funding of chemotherapy**

In combination with chlorambucil for previously untreated patients with CD20 positive chronic lymphocytic leukaemia (CLL) and comorbidities, defined as a total cumulative illness rating scale (CIRS) score >6, or creatinine clearance (CrCl) <70 mL/min or both.

#### Note:

1 script +7 repeats

Not to be used as monotherapy

- 2.1 Listing was requested on the basis of a cost-utility analysis with two analyses presented: 1. obinutuzumab plus chlorambucil compared to chlorambucil monotherapy; and 2. obinutuzumab plus chlorambucil compared to rituximab plus chlorambucil.
- 2.2 The ESC and DUSC noted that there is potential for patients who are 'medically fit' to be considered eligible for obinutuzumab because: the cumulative illness rating scale (CIRS) involves assessments that may be considered to be subjective; assessment of co-morbidity 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. The Pre-PBAC response argued that there is currently no alternative to the CIRS score to assess co-morbidity.
- 2.3 To help limit obinutuzumab use to the intended population, the Pre-Sub-Committee Response (PSCR) and Pre-PBAC response proposed that the PBS restriction could:
- include a criterion that the patient is ineligible for fludarabine;
  - specifically exclude 'medically frail' patients (CrCL<30mL/min);
  - explicitly state that the CIRS score must exclude CLL-induced illness or organ damage.

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

### 3 Background

- 3.1 Obinutuzumab is an anti-CD20 monoclonal antibody that was registered by the TGA on 15 May 2014 for use in combination with chlorambucil, for the treatment of patients with previously untreated CLL.
- 3.2 Obinutuzumab has not previously been considered by the PBAC.

- 3.3 Rituximab, the first registered anti-CD20 monoclonal antibody, is PBS-listed for the treatment of patients with CD20 positive CLL in combination with fludarabine and cyclophosphamide (FC) (recommended at the November 2010 PBAC meeting). However, rituximab is not currently PBS-listed for CLL for the broader indication of use 'in combination with chemotherapy' (i.e. chemotherapy other than FC), despite being recommended in this setting by the PBAC in January 2011. The sponsor had proposed a ■% price decrease for this listing. A risk-share arrangement is yet to be developed and agreed upon.

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

#### **4 Clinical place for the proposed therapy**

- 4.1 The submission proposed that the place in therapy for obinutuzumab is, in combination with chlorambucil, as first-line treatment for previously untreated, unfit patients with CD20 positive CLL and comorbidities. The comorbidities are defined as a total CIRS score of more than six, or creatinine clearance (CrCl) <70 mL/min, or both.

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

#### **5 Comparator**

- 5.1 The submission nominated two comparators:
1. chlorambucil monotherapy as the primary comparator;
  2. rituximab plus chlorambucil as the secondary comparator.
- 5.2 The ESC agreed that chlorambucil monotherapy was an appropriate comparator. Further, the ESC agreed with the PSCR that rituximab plus chlorambucil was also a relevant comparator.
- 5.3 The PSCR provided market research data showing that an increasing proportion of Australian patients with CLL and at least one comorbidity are being treated with rituximab-containing regimens other than FCR. In 2013-14, ■% of CLL treatment regimens in patients with comorbidities were categorised as 'rituximab ± chlorambucil and other rituximab-containing regimens' (i.e. other than FCR lite) compared to ■% in 2011-12 (IPSOS Australian market research data). The data does not specify whether such use is being supplied under the PBS.

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

#### **6 Consideration of the evidence**

##### ***Sponsor hearing***

- 6.1 The sponsor did not request a hearing for this item.

##### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from five individuals, two healthcare professionals and four organisations; Lymphoma Australia, the Medical Oncology Group of Australia and Private Cancer Physicians of Australia (joint submission), and the Haematology Society of Australia and New Zealand (two letters). The comments highlighted that obinutuzumab provides a treatment option for older 'less fit' patients with CLL and prolongs remission during which time patients can live 'a normal life'.

6.3 The PBAC noted that this advice was supportive of the evidence provided in the submission.

**Clinical trials**

6.4 The submission presented the results of one trial, CLL11. This was an open-label randomised trial that compared:

- Stage 1a: obinutuzumab plus chlorambucil to chlorambucil monotherapy.
- Stage 1b: rituximab plus chlorambucil to chlorambucil monotherapy.
- Stage 2: obinutuzumab plus chlorambucil to rituximab plus chlorambucil.

6.5 The submission was based on the May 2013 data-cut of CLL11, which had a median duration of follow-up of 22.8 months for Stage 1a and 18.7 months for Stage 2. The PSCR and pre-PBAC responses provided information regarding a more recent data-cut (3 March 2014) which provided around 9 months of additional follow-up (i.e. median duration of follow-up of 31.8 months for Stage 1a and 27.3 months for Stage 2). Where available, the more recent data is used in these Minutes.

6.6 Details of the CLL11 trial, as provided in the submission, are presented in the tables below.

**Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trial(s)</b>		
CLL11	<p>Primary Clinical Study Report - BO21004/CLL11 - Stage 1a (GC1b vs. C1b) – An open-label, multi-centre, three arm randomized, phase III study to compare the efficacy and safety of RO5072759 + chlorambucil (GC1b), rituximab + chlorambucil (RC1b) or chlorambucil (C1b) alone in previously untreated CLL patients with comorbidities. Research Report Number 1038127.</p> <p>Update Clinical Study Report – BO21004: Stage 1a – 1b Update. An open-label, multicentre, three arm randomized, phase III study to compare the efficacy and safety of RO5072759 + chlorambucil (GC1b), rituximab + chlorambucil (RC1b) or chlorambucil (C1b) alone in previously untreated CLL patients with comorbidities. Research Report Number 1057363.</p> <p>Primary Clinical Study Report – BO21004/CLL11 – Stage 2 (GC1b vs. RC1b) – An open-label, multi-centre, three arm randomized, phase III study to compare the efficacy and safety of RO5072759 + chlorambucil (GC1b), rituximab + chlorambucil (RC1b) or chlorambucil (C1b) alone in previously untreated CLL patients with comorbidities. Research Report Number 1056550.</p> <p>Goede V, Fischer K, Busch R et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions.</p>	<p>March 2013</p> <p>December 2013</p> <p>December 2013</p> <p>N Eng J Med 2014 Jan 8 [Epub ahead of print]</p>

Source: Table B.2.3. pp.7-8 of the submission.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
<b>Obinutuzumab +chlorambucil vs. chlorambucil</b>						
CLL11 Stage 1a	356	R, OL, MC median follow-up 22.8 months in submission (31.8 months in Pre-PBAC response)	Unclear	Previously untreated CLL with comorbidities	PFS, OS (secondary)	Yes
<b>Obinutuzumab +chlorambucil vs. rituximab +chlorambucil</b>						
CLL11 Stage 2	663	R, OL, MC median follow-up 18.7 months in submission (27.3 months in Pre-PBAC response)	Unclear	Previously untreated CLL with comorbidities	PFS, OS (secondary)	Yes

MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised; Source: compiled during the evaluation.

- 6.7 The primary outcome from CLL11 was progression-free survival (PFS) as assessed by the site investigators. Secondary outcomes included overall survival (OS), quality of life and time to new anti-leukaemia treatment.
- 6.8 The comparative efficacy of obinutuzumab plus chlorambucil was investigated in Stages 1a and 2 of the trial:
- In Stage 1a of CLL11, 356 patients were randomised 2:1 to obinutuzumab plus chlorambucil versus chlorambucil monotherapy. 25.4% of the chlorambucil monotherapy patients crossed over to obinutuzumab plus chlorambucil treatment.
  - In Stage 2 of CLL11, 663 patients were randomised 1:1 to obinutuzumab plus chlorambucil versus rituximab plus chlorambucil. Cross-over was not permitted in this stage.
- 6.9 In Stage 1b of CLL11, 351 patients were randomised 2:1 to rituximab plus chlorambucil versus chlorambucil monotherapy. At median follow-up of 22.7 months, rituximab plus chlorambucil resulted in 16.3 months median PFS, compared to 11.1 months in the chlorambucil monotherapy arm (PFS HR:0.44,  $p < 0.001$ ). Overall survival was not statistically significantly improved (OS HR: 0.66 (95% CI: 0.39-1.11;  $p = 0.11$ ). However, this arm of the trial may have been underpowered for this comparison (it was powered [80%] to detect a HR of 0.6), and 25.4% of the chlorambucil monotherapy patients crossed over to obinutuzumab plus chlorambucil treatment.

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

### **Comparative effectiveness**

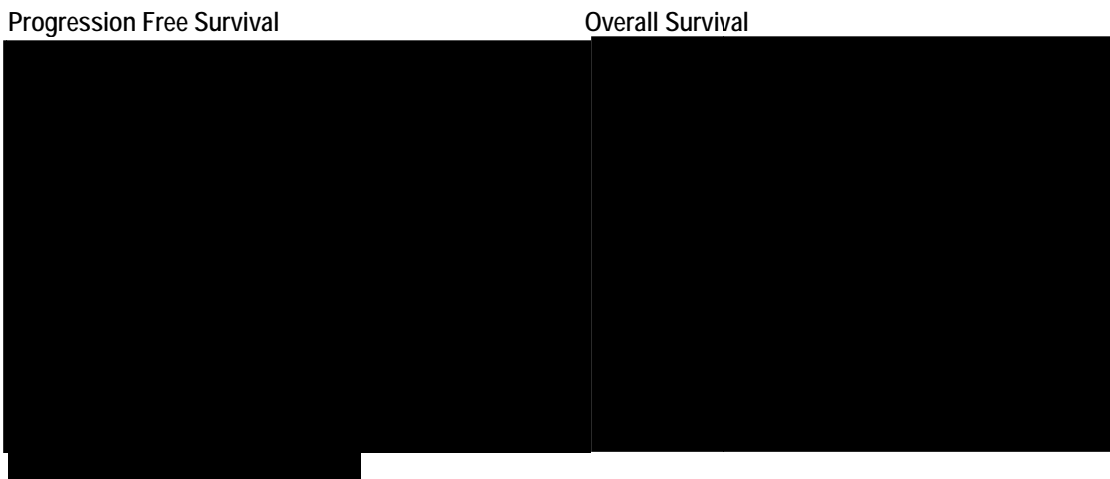
- 6.10 The table and Kaplan-Meier plots below show the comparative effectiveness of obinutuzumab plus chlorambucil compared to chlorambucil monotherapy (Stage 1a).

Key results of obinutuzumab plus chlorambucil versus chlorambucil monotherapy in CLL11 (Stage 1a)

	Obinutuzumab +chlorambucil n with event/N (%)	Chlorambucil n with event/N (%)	RD (95% CI)	Hazard ratio (95% CI)
<b>Progression free survival (investigator assessed)</b>				
14.2 mths follow-up	52/238 (21.8%)	71/118 (60.2%)	-38.3 (-48.6, -28.0)	0.14 (0.09, 0.21)
22.8 mths follow-up	93/238 (39.1%)	96/118 (81.4%)	-42.3 (-51.6, -32.9)	0.18 (0.13, 0.24)
█ mths follow-up	█ %	█ %	█	█
█ mths follow-up	█ months <sup>a</sup>	█ months <sup>a</sup>		
Median time to progression <sup>a</sup>				
<b>Overall survival</b>				
14.2 mths follow-up	13/238 (5.5%)	9/118 (7.6%)	-2.2 (-7.8, 3.4)	0.68 (0.29, 1.60)
22.8 mths follow-up	22/238 (9.2%)	24/118 (20.3%)	-11.1 (-19.2, -3.0)	0.41 (0.23, 0.74)
█ mths follow-up	█ %	█ %		█

Source: Table B.6.1 p.64, Table B.6.2, p.69, and Table B.6.9, p89-90 of the submission; █  
 data-cut █ aKaplan-Meier estimates  
 Bold=statistically significant; italics = calculated during evaluation;

Figure: Kaplan-Meier plots of Progression Free Survival (Investigator assessment) and Overall Survival – Stage 1a Update (ITT)



- 6.11 A statistically significant improvement in PFS and OS (at 22.8 and █ months follow-up) was observed for obinutuzumab plus chlorambucil compared to chlorambucil monotherapy. At █ months the HR for PFS was █ (95% CI: █) and the HR for OS was █.
- 6.12 The ESC considered the chlorambucil dose in the CLL11 trial was at the lower end of usual practice (█ mg per cycle, compared to █ mg which was suggested as an appropriate dose for CLL patients with comorbidities by █ Australian clinicians). The ESC noted data from the literature that suggested that a higher chlorambucil dose per cycle may result in longer PFS. Thus the ESC considered that the use of lower doses in the monotherapy arm may have led to an underestimation of PFS in this arm of the trial, compared to the benefits that would be seen in clinical practice. The chlorambucil doses used in combination with obinutuzumab in the trial are likely to reasonably reflect the doses that will be used in clinical practice due to risk-benefit trade-offs when used in combination. Thus, the ESC considered that the incremental efficacy of obinutuzumab plus chlorambucil compared to chlorambucil monotherapy may have been overestimated in the trial.

- 6.13 The PSCR argued that there is no established optimal chlorambucil dose and that reduced doses are recommended for elderly patients with significant comorbidities. Further, the PSCR and pre-PBAC responses argued that the relationship between the median chlorambucil dose per cycle and PFS in CLL was based on the chlorambucil dose per cycle, and did not consider the total cumulative chlorambucil dose administered. The PSCR further argued that there is no conclusive randomised controlled trial evidence to establish any relationship between chlorambucil dose and PFS.

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

- 6.14 The table and Kaplan-Meier plots below show the comparative effectiveness of obinutuzumab plus chlorambucil compared to rituximab plus chlorambucil (Stage 2).

Key results of obinutuzumab plus chlorambucil versus rituximab plus chlorambucil in CLL11 Stage 2

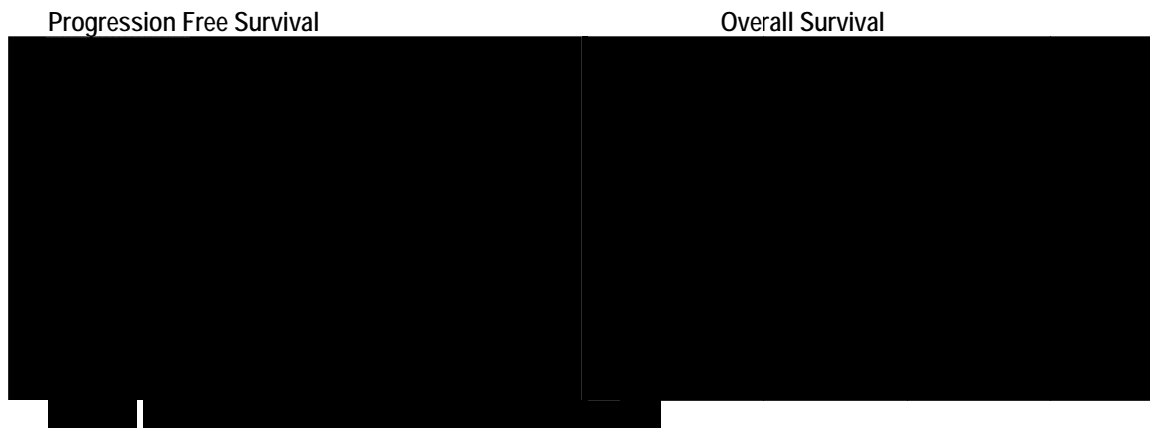
	Obinutuzumab +chlorambucil (N=333)	Rituximab +chlorambucil N=330	RD (95% CI)	HR (95% CI)
<b>18.7 month follow-up</b>				
PFS, disease progression (investigator assessed)	██████████%	██████████%	████	██████████
Median time to progression, <sup>a</sup> months	██████████ months <sup>a</sup>	██████████ months <sup>a</sup>		
Time To Next Therapy, n with event (%)	██████████%	██████████%	████	
Median Time To Next Therapy <sup>a,b</sup>	██████████ months <sup>a</sup>	██████████ months <sup>a</sup>		██████████
<b>Overall survival</b>				
Overall survival (18.7 month follow-up), n with event (%)	28 (8.4%)	41 (12.4%)		0.66 (0.41, 1.06)
Overall survival (████ month follow-up), n with event (%)	██████████%	██████████%	████	██████████

Source: ██████████

a Kaplan-Meier estimates; b time to new anti-leukemia treatment

RD = risk difference; NNT = number needed to treat; PFS = progression free survival; CI = confidence interval; bold = statistically significant

Figure: Kaplan-Meier Plots of Progression Free Survival (Investigator assessed) and Overall Survival – Stage 2 update (ITT)



- 6.15 A statistically significant improvement in PFS was observed for obinutuzumab plus chlorambucil compared to rituximab plus chlorambucil. At [redacted] months there was a [redacted]% risk difference in PFS (HR [redacted] [redacted to redacted]) favouring obinutuzumab plus chlorambucil. Median OS result has not been reached with [redacted]% and [redacted]% of patients having died in the obinutuzumab plus chlorambucil, and the rituximab plus chlorambucil arms, respectively. The ESC noted that while the hazard ratio for OS was not statistically significant, the trend was in favour of obinutuzumab plus chlorambucil.

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

**Comparative harms**

- 6.16 The CLL11 trial results show the obinutuzumab arm has 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. While the submission stated that the adverse events associated with obinutuzumab were manageable, the ESC noted the higher incidence of grade 3 to 5 reactions (as outlined in the discussion of benefits and harms below).
- 6.17 A summary of the comparative benefits and harms for obinutuzumab plus chlorambucil versus chlorambucil is presented in the table below.

Summary of comparative benefits and harms for obinutuzumab plus chlorambucil and chlorambucil – CLL11 trial (Stage 1a)

Benefits- median [redacted] months follow-up						
Median [redacted] months follow-up	Obinutuzumab +chlorambucil	Chlorambucil	HR (95% CI)			
Progressed <sup>a</sup>	Median time to progression: [redacted] months	Median time to progression: [redacted] months	[redacted]			
OS (patients died)	[redacted]	[redacted]%	[redacted]			
Harms – based on median follow-up at 22.8 months						
Grade 3 to 5	Obinutuzumab +chlorambucil	Chlorambucil	RR (95% CI)	Event rate/100 patients/22.8 months		RD (95% CI)
				Obinutuzumab +chlorambucil	Chlorambucil	
Infusion-related reactions	51/241	0/116	49.3 (3.07, 792)	21	0	0.21 (0.16, 0.26)
Neutropenia	82/241	18/116	2.20 (1.39, 3.49)	34	17	0.19 (0.10, 0.27)
Thrombocytopenia	26/241	4/116	3.14 (1.12, 8.79)	11	3	0.07 (0.02, 0.13)

Abbreviations: RD = risk difference; RR = risk ratio; HR = hazard ratio; CI = confidence interval

<sup>a</sup>Kaplan-Meier estimates

Source: Compiled during the evaluation (italics)/Table B.6.1-B.6.2 p.64,69 of the submission.

- 6.18 On the basis of direct evidence presented by the submission and the pre-PBAC response, the comparison of obinutuzumab plus chlorambucil and chlorambucil monotherapy resulted in:
- An improvement in median PFS of [redacted] additional months.

- 6.19 On the basis of direct evidence presented by the submission, for every 100 patients treated with obinutuzumab plus chlorambucil, in comparison to chlorambucil monotherapy, over a 22.8 months median duration of follow-up there would be:
- Approximately 21 additional grade 3 to 5 infusion-related reactions;
  - Approximately 17 additional episodes of grade 3 to 5 neutropenia, but no additional episodes of infection (all-Grade infection);
  - Approximately 8 additional episodes of grade 3 to 5 thrombocytopenia.
- 6.20 A summary of the comparative benefits and harms for obinutuzumab plus chlorambucil versus rituximab plus chlorambucil is presented in the table below.

Summary of comparative benefits and harms for obinutuzumab plus chlorambucil and rituximab plus chlorambucil – CLL11 trial (Stage 2)

Benefits – median [redacted] months follow-up						
median [redacted] months follow-up	Obinutuzumab +chlorambucil	Rituximab +chlorambucil		RD (95% CI)	HR (95% CI)	
Progressed	[redacted] %	[redacted] %				
OS (patients died)	[redacted] %	[redacted] %				
Harms – median 18.7 months follow-up						
Grade 3 to 5	Obinutuzumab +chlorambucil	Rituximab +chlorambucil	RR (95% CI)	Event rate/100 patients/18.7 months		RD (95% CI)
				Obinutuzumab +chlorambucil	Rituximab +chlorambucil	
Infusion-related reactions	66/336	12/321	5.25 (2.90, 9.53)	20	4	0.16 (0.11, 0.21)
Neutropenia (Grade 4-5) <sup>a</sup>	59/336	35/321	1.61 (1.09, 2.38)	18	11	0.07 (0.01, 0.12)
Thrombocytopenia	35/336	10/321	3.34 (1.68, 6.64)	10	3	0.07 (0.04, 0.11)

Abbreviations: RD = risk difference; RR = risk ratio; HR = hazard ratio; CI = confidence interval

Source: Section B.6 of the submission [redacted]

- 6.21 On the basis of direct evidence presented by the submission, the comparison of obinutuzumab plus chlorambucil and rituximab plus chlorambucil over a median follow-up of [redacted] months, resulted in:
- An improvement in median PFS of [redacted] months.
  - Approximately [redacted] fewer patients per 100 having progressed.
  - Approximately [redacted] fewer patients per 100 requiring further anti-leukemia therapy.
- 6.22 On the basis of direct evidence presented by the submission, for every 100 patients treated with obinutuzumab plus chlorambucil, in comparison to rituximab plus chlorambucil, over a median duration of follow-up of 18.7 months, there would be:
- Approximately 16 additional grade 3 to 5 infusion-related reactions;
  - Approximately 7 additional episodes of grade 4 neutropenia but no additional episodes of infection (all-Grade infection);
  - Approximately 7 additional episodes of grade 3 to 5 thrombocytopenia.

**Clinical claim**

- 6.23 The submission describes obinutuzumab plus chlorambucil as superior in terms of comparative effectiveness and inferior in terms of comparative safety over

chlorambucil alone. The ESC considered that the clinical claims were supported by the evidence from the key trial, however the extent of the benefit, in terms of both comparative effectiveness and safety, may have been overestimated for Australian clinical practice because the chlorambucil dose was at the lower end of usual practice.

- 6.24 The submission describes obinutuzumab plus chlorambucil as superior in terms of comparative effectiveness and inferior in terms of comparative safety over rituximab plus chlorambucil. The ESC considered that the claim was supported for PFS, but not for OS where the hazard ratio at 18.7 months follow-up was not statistically significant (HR: 0.66; 95% CI: 0.41 to 1.06).

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

**Economic analysis**

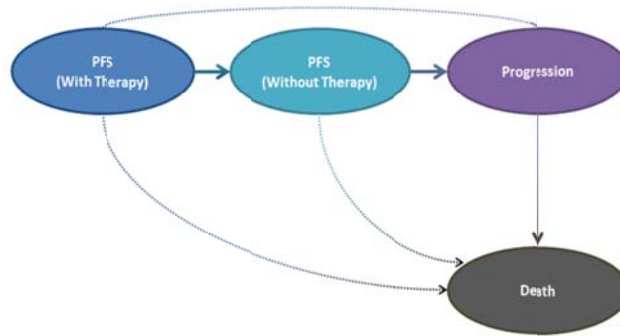
- 6.25 The submission presented a cost-utility analysis that resulted in an incremental cost per quality adjusted life year (QALY) of \$45,000/QALY - \$75,000/QALY compared to chlorambucil monotherapy and \$45,000/QALY - \$75,000/QALY compared to rituximab plus chlorambucil. These were based on the May 2013 data-cut of CLL11.
- 6.26 The PSCR and pre-PBAC responses updated the economic model using inputs from the more recent data-cut (3 March 2014). The PSCR base case maintained the same model structure and other assumptions as used in the submission, and resulted in an incremental cost per QALY of \$15,000/QALY - \$45,000/QALY compared to chlorambucil monotherapy (or \$15,000/QALY - \$45,000/QALY using the best-fitting tail for PFS).

Summary of model structure and rationale

Component	Summary
Time horizon	10 years extrapolated from CLL11 data
Outcomes	QALYs, LYs, costs
Methods used to generate results	Markov model, cohort expected value analysis, extrapolated trial data
Health states	Progression-free during treatment, progression-free after treatment, progression, death
Cycle length	1 week with half-cycle correction
Transition probabilities	CLL11 for PFS and CLL5 for PPS, extrapolation as discussed in the commentary

Source: compiled during the evaluation;  
PFS = progression-free survival; PPS = post-progression survival; QALY = quality-adjusted life year; LY = life year;

Structure of economic model (as provided in the submission)



Source: Figure D.3.1 p. 8 of the submission.

While not depicted in the figure, patients can stay in the same health state for more than one cycle.)

6.27 The submission presented stepped economic evaluations for each of the comparators. Details are summarised in the tables below.

Results of the stepped economic evaluation: obinutuzumab + chlorambucil versus chlorambucil – based on May 2013 data-cut, as presented in the submission.

Step and component	Obinutuzumab +chlorambucil	Chlorambucil	Increment
<b>Step 1: trial-based costs and outcomes</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
<b>Step 2: parametric extrapolation from 22.8 over a 10 year time horizon</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
<b>Step 3: inclusion of MRU costs</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
<b>Step 4: inclusion of AE costs</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
<b>Base case (including incorporation of [REDACTED] % rebate for obinutuzumab)</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]

Source: Tables D.5.1-6 pp.20-25 of the submission.

QALY = quality adjusted life year; MRU = medical resource utilisation (progression free health state only)

Table 8: Results of the stepped economic evaluation – obinutuzumab plus chlorambucil versus rituximab plus chlorambucil

Step and component	Obinutuzumab +chlorambucil	Rituximab +chlorambucil	Increment
<b>Step 1: trial-based costs and outcomes</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYs	[REDACTED]	[REDACTED]	[REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra LY gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
<b>Step 2: parametric extrapolation from 18.7 months over a 10 year time horizon</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYs	[REDACTED]	[REDACTED]	[REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra LY gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
<b>Step 3: inclusion of MRU costs</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYs	[REDACTED]	[REDACTED]	[REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra LY gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
<b>Step 4: inclusion of AE costs</b>			
Costs	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
LYs	[REDACTED]	[REDACTED]	[REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra LY gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
<b>Base case (incorporation of [REDACTED] % rebate for obinutuzumab)</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYs	[REDACTED]	[REDACTED]	[REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra LY gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]

Source: Tables D.5.1-6 pp.20-25 of the submission.

- 6.28 For the modelled economic evaluation against rituximab plus chlorambucil, the comparator rituximab price used in the submission was the price proposed by the sponsor when rituximab was recommended for use in this indication. This price was used as a means of representing the value of rituximab in this setting.
- 6.29 The ESC considered that the incremental cost-effectiveness ratio (ICER) of \$45,000/QALY - \$75,000/QALY for obinutuzumab plus chlorambucil versus chlorambucil was unreliable because:
1. The low chlorambucil dose used in monotherapy in the clinical trial may have underestimated PFS in this treatment arm. The PSCR attempted to account for this in sensitivity analyses by adjusting the HR by [REDACTED] for (a) both the treatment arms; and (b) just the chlorambucil monotherapy arm. The ESC considered that the latter sensitivity analysis (i.e. only adjusting the HR for the monotherapy arm) was more informative because in clinical practice lower chlorambucil doses may be used in combination with obinutuzumab. The ESC noted that the PSCR provided no justification for the use of the [REDACTED] adjustment value.

2. The model structure does not appropriately reflect paths of disease progression, including the possibility of additional lines of treatment, with their costs and health benefits. The potential for additional lines of treatment was also noted by the Haematology Advisory Board which was quoted in the submission as stating that ■% of unfit CLL patients with comorbidities would receive 2 or more lines of therapy. The ESC considered that the model should have accounted for treatment post-progression, particularly given the potential for use of rituximab-based regimens in later lines of treatment.

The PSCR (pg 3) argued that a more complex model would require a number of assumptions for which there are no reliable data, and that subsequent lines of treatment are inherently captured by using the CLL5 data to extrapolate OS. The PSCR attempted to account for post-progression treatment in a sensitivity analysis in which the costs and utilities of second-line rituximab therapy were applied at the time of patient progression. The adjustment was simplistic, for example it did not include any differences in OS resulting from second-line therapy. The ESC considered that new health state/s would need to be incorporated into the model to reliably capture the impacts of treatment post progression.

3. The extrapolation of OS beyond the trial duration may not be reasonable. The model estimated OS by applying post-progression survival data from the CLL5 trial. The CLL5 trial compared chlorambucil with fludarabine, and recruited patients from 1999 to 2004. The ESC considered that the CLL5 trial data might not reflect current clinical practice and the improved efficacy of additional lines of treatment (which is not captured in the model structure). This model appeared to under-estimate OS in both arms of the model. The modelled OS for obinutuzumab plus chlorambucil and chlorambucil monotherapy at 10 years (■■% and ■■%, respectively) is less than observed in the long-term follow up of CLL5 and also in registry data (eg. 10-year survival in American CLL patients aged 75 and older is 37.6%). While acknowledging that patients included in the registries may not be representative of the trial population (PSCR, pg 4), the ESC concluded that OS is underestimated in both arms, and that this favours obinutuzumab. To attempt to account for this issue, the PSCR included a sensitivity analysis that decreased the probability of post-progression death by a factor of ■■.

Further, the ESC noted that time to progression is the primary driver of effectiveness differences in the model because the same mortality rate is applied to both arms for progressed patients. The OS curves do not converge over the 10-year time horizon of the model.

4. The ESC considered that the cost of adverse events were under-estimated in the model because events that were deemed to be either 'non-serious' or not of 'special interest' were not included. The ESC considered that the exclusion of these costs was inappropriate given the high incidence of grade 3-5 adverse events in the obinutuzumab arm, and was likely to favour obinutuzumab. The PSCR and pre-PBAC response included costs for cardiac adverse events and serious leucopenia.

6.30 The ESC also noted that:

- the 10-year time horizon used in the model may not adequately reflect the length of survival of CLL patients who are older and/or have co-morbidities that has been shown in observational data and CLL5. In its previous

considerations of rituximab, the PBAC had considered that a 10-year time horizon was appropriate in CLL patients who are older and have other comorbidities (rituximab public summary document March 2010).

- Patient-reported outcomes using the QLQ-C30 questionnaire were collected in CLL11 but were not used in the economic model. The submission did not justify this. The ESC noted that published mapping algorithms are available and considered that it would have been informative for the results to have been presented.

6.31 The ESC noted that the PSCR provided sensitivity analyses to attempt to account for many of the issues outlined above. The ESC noted that the analyses were based on arbitrary parameter values and may not provide a reliable basis for decision-making. The ESC considered that the most informative scenario included all changes (i.e. an adjustment to the HR of [REDACTED] in the chlorambucil arm only, application of costs and utilities of second-line rituximab at the time of patient progression, and a decrease in the weekly probability of post-progression death by a factor of [REDACTED]. This resulted in an ICER of \$45,000/QALY - \$75,000/QALY for the comparison against chlorambucil monotherapy based on the datacut presented in the submission.

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

**Drug cost/patient:** estimated [REDACTED], based on net cost to PBS after rebate, offsets and patient co-payments, assuming an average of [REDACTED] scripts per patient.

#### ***Estimated PBS usage & financial implications***

6.32 The submission was considered by the Drug Utilisation Sub-Committee (DUSC). The DUSC considered that the estimates presented in the submission to be underestimated. The DUSC considered that the main issues were:

- Patient numbers are likely to be underestimated, particularly in years 1 and 2, due to inadequate capture of the prevalent population who may be treated. The PBAC agreed that, should obinutuzumab be PBS-listed, then there may be some watch and wait patients who may be treated earlier than they are currently.
- The interpretation of comorbidities in clinical practice may be broader than in the clinical trial and as proposed in the restriction (CIRS score >6 could be interpreted as including CLL rather than in addition to CLL). This may result in a higher than expected number of patients treated.
- The submission does not assume any uptake for those patients with CLL who are treated with low dose fludarabine with cyclophosphamide and rituximab (FCR-lite).
- Further, the submission does not assume any uptake for those patients with CLL who are currently not treated. This may underestimate the uptake. The Pre-PBAC response from the sponsor argued that treatment was inappropriate in the very elderly and very frail, and so this was not a major issue.
- The cost offsets may be overestimated because of assumed reductions in the use of rituximab (without fludarabine plus cyclophosphamide) that lie outside the PBS listing for rituximab. The pre-PBAC response provided revised financial estimates which removed these cost-offsets.
- Cost offsets would also not be realised if the listing resulted in a change in the algorithm leading to sequential therapy with rituximab.

- DUSC considered that there is potential for retreatment with obinutuzumab and potential for obinutuzumab to be used after relapse or progression on other treatments.
- Financial estimates rely almost entirely on clinician opinion and market research.
- Potential for use of obinutuzumab outside of the requested PBS restriction in healthier patients (total CIRS score of six or less) or patients with disease other than CLL (e.g. non-Hodgkin’s lymphoma).

6.33 The estimated PBS usage and financial implications are presented in the table below.

**Estimated use and financial implications – per DUSC advice**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Number treated	█	█	█	█	█
Market share <sup>a</sup>	█%	█%	█%	█%	█%
Scripts <sup>b</sup>	█	█	█	█	█
<b>Estimated net cost to PBS/RPBS/MBS</b>					
Net PBS Cost of obinutuzumab <sup>c</sup>	█	█	█	█	█
Net PBS cost of listing new drug less █% rebate	█	█	█	█	█
Net cost to PBS including substitution <sup>d</sup>	█	█	█	█	█
Net cost to MBS	█	█	█	█	█
Cost to State and Territory health budget services <sup>e</sup>	█	█	█	█	█
Estimated total net cost	█	█	█	█	█

<sup>a</sup> Weighted for different uptake for current treatments:

- █% for patients currently treated with chlorambucil, rituximab plus chlorambucil, rituximab with other treatments)
- █% for patients currently untreated or treated with rituximab plus fludarabine and cyclophosphamide
- █% for other chemotherapy regimens

<sup>b</sup> Assuming █ per year as estimated by the submission.

<sup>c</sup> Cost to PBS based on weighted DPMQ (DPMQ weighted for public:private hospital use); net of patient co-payments.

<sup>d</sup> The post-rebate cost minus cost offsets (additional cost for pre-medications and chlorambucil; reduced cost for rituximab).

<sup>e</sup> Revised using inputs from Item 5.10 Financial Cost to PBS\_PSCR (IPSOS 2013).xls (corrected); see Appendix A.

Source: Table 7 p.6 of the commentary, updated from revised spreadsheet Item 5.10 Financial Cost to PBS\_PSCR (IPSOS 2013).xls (corrected).

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

**7 PBAC Outcome**

7.1 The PBAC rejected the submission to list obinutuzumab on the PBS for the treatment of CLL in patients with comorbidities as the submission failed to demonstrate that obinutuzumab was cost effective. The PBAC agreed with the ESC that the economic model submitted by the sponsor was unsuitable as a basis for determining the cost-effectiveness of obinutuzumab in the requested treatment setting. The reasons for this are outlined in paragraphs 7.11 to 7.17 below.

- 7.2 The PBAC reaffirmed its recommendation of January 2011 (out-of-session) to list rituximab for the treatment of CD20 positive CLL in combination with chemotherapy. The PBAC expressed concern that rituximab remained unlisted in this setting, and:
- noted that the results of Stage 1b of CLL11, which compared rituximab plus chlorambucil to chlorambucil monotherapy, supported the PBAC's January 2011 recommendation to list rituximab in this setting.
  - noted that the PSCR had provided market research data indicating extensive use of rituximab in combination with chemotherapies other than FC in patients with CLL.
  - recalled its concerns from March 2010 and November 2010 that restricting subsidised rituximab use to combination with FC only may not be ideal clinically, stating that "if the PBS listing of rituximab was restricted to use with FC alone there may be toxicity issues with use of this combination in the elderly." (paragraph 4.1.33, Ratified Minutes November 2010)
- 7.3 The PBAC considered that there is a clinical need for treatment options for patients with CLL with comorbidities. The PBAC welcomed and noted the input received from individuals, health care professionals and organisations in support of the submission for obinutuzumab. The comments highlighted that obinutuzumab prolongs remission during which time patients can live 'a normal life' and provides a treatment option for older 'less fit' patients with CLL.
- 7.4 The PBAC considered that the place in therapy proposed by the submission for obinutuzumab was appropriate, noting that the submission pertained to those patients who require therapy and focused on patients considered to be unfit for FC. The PBAC considered that obinutuzumab should be restricted to use in patients who are previously untreated, as proposed in the submission.
- 7.5 The PBAC considered that the obinutuzumab restriction should be based around the trial inclusion and exclusion criteria, including requiring patients to have a total CIRS score >6 (excluding CLL-induced illness or organ damage) and/or a creatinine clearance <70 mL/min.
- 7.6 The PBAC considered that chlorambucil monotherapy, and rituximab plus chlorambucil were both appropriate comparators.
- 7.7 The PBAC noted the ESC's concerns regarding the dose of chlorambucil administered in the monotherapy arm of the CLL11 trial, but agreed with the sponsor that the chlorambucil dosing used in the trial was applicable to Australian clinical practice in the relevant group of patients with co-morbidities. Australian guidelines (such as the eviQ treatment protocol) recommend the use of lower chlorambucil doses in elderly patients with co-morbidities.
- 7.8 The PBAC considered that time to next anti-leukemia therapy, which was a secondary outcome of CLL11, was an important, patient relevant outcome. The PBAC noted that, on average, there was a considerable length of time between a patient progressing and requiring their next anti-leukemia therapy - in the obinutuzumab plus chlorambucil arm the difference between median PFS and median time to next therapy was ■■■ months, and in the rituximab plus chlorambucil arm the difference was ■■■ months.
- 7.9 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.

- 7.10 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 trend was in favour of obinutuzumab plus chlorambucil and the more recent data is approaching statistical significance [REDACTED].
- 7.11 The PBAC noted that there were a number of aspects of the economic model that led to its conclusion that the economic model submitted by the sponsor was unsuitable as a basis for determining the cost-effectiveness of obinutuzumab in the requested treatment setting.
- 7.12 Firstly, the PBAC agreed with the ESC that a key issue with the model was the method used to derive the probability of post-progression survival, which used data from the CLL5 trial. In particular, the PBAC noted that for the comparison against rituximab plus chlorambucil, the OS curve generated from the updated Markov model (provided in the PSCR) does not match the OS observed in CLL11 when the most recent data cut is used (Kaplan-Meier curves, CSR for CLL11 3 March 2014 pg 45). The PBAC concluded that it was not possible to interpret the ICER for the comparison against rituximab plus chlorambucil because of this inconsistency between the modelled and observed OS.
- 7.13 Secondly, the PBAC considered that the structure of the economic model did not appropriately reflect different levels of disease progression. In the submission's model, patients transition from the "progression-free without treatment" health state to "progressive disease". The PBAC considered that the model required an additional health state to account for patients who are progressed but well (i.e. patients who have progressed but do not need therapy for CLL). The PBAC 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 without treatment" and "progressive disease" health states, which had utility weights of 0.82 and 0.66, respectively.
- 7.14 Thirdly, the PBAC agreed with the ESC that 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. The PBAC's views were supported by both the submission's Haematology Advisory Board who stated that [REDACTED]% of unfit CLL patients with co-morbidities would receive 2 or more lines of therapy, and the results of the CLL11 trial which found that a considerable proportion of patients required re-treatment with anti-leukemia therapy ([REDACTED]% of patients in the obinutuzumab plus chlorambucil arm, and [REDACTED]% of patients in the rituximab plus chlorambucil arm at 27.3 months of follow-up). The PBAC considered that new health state/s would need to be incorporated into the model to adequately account for this impact. The PBAC acknowledged the advice in the pre-PBAC response that additional assumptions would need to be made, and that this change is likely to favour obinutuzumab. However, the PBAC considered that a reliable model structure would need to appropriately reflect the possibility of additional lines of treatment, with their costs and health benefits.
- 7.15 Fourthly, the PBAC noted that the model was highly sensitive to the choice of parametric function used to extrapolate PFS when the more recent data cut is used. For example, the ICER/QALY for the comparison against chlorambucil monotherapy was \$15,000/QALY – 45,000/QALY when a Gompertz tail for obinutuzumab plus

chlorambucil and a gamma tail for chlorambucil monotherapy are used, while the ICER/QALY is \$15,000/QALY - \$45,000/QALY when the log-logistic tail (which is best-fitting) is used in both arms. Further, the PBAC noted that use of the more recent data cut significantly reduced the ICER/QALY from \$45,000/QALY - \$75,000/QALY to \$15,000/QALY – 45,000/QALY (best-fitting tail for PFS) for the comparison against chlorambucil monotherapy. This further reinforced PBAC's concerns regarding the reliability of the model.

- 7.16 The PBAC acknowledged that attempts had been made to account for some of these issues in the PSCR and Pre-PBAC responses. However, the PBAC agreed with the ESC that these adjustments were based on arbitrary parameter values and did not appropriately account for the issues identified, which would require the incorporation of additional health states and data into the Markov model.
- 7.17 The PBAC considered that an appropriate model would:
- Include a progressed but well health state with an appropriate utility value;
  - Include post-progression therapy in the base case, with this excluded in a sensitivity analysis;
  - Ensure modelled OS is consistent with the trial-based data;
  - Include the costs of adverse events (noting that the costs of cardiac adverse events and serious leucopenia had been included in the PSCR and the pre-PBAC response); and
  - Use a 10 year time horizon, per the submission. The PBAC considered that this time horizon was appropriate for the relevant population of patients with multiple co-morbidities.
- 7.18 The PBAC noted the other concerns about the model that were raised by the ESC. In this case, the PBAC accepted the use of utilities from the literature rather than the trial.
- 7.19 The PBAC agreed with DUSC that it is 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.
- 7.20 The PBAC considered that this risk of use of obinutuzumab outside the requested restriction would be particularly high in the absence of suitable, alternative PBS-listed treatment options for patients with CLL who cannot tolerate a fludarabine-based regimen. Therefore the PBAC considered that, should rituximab remain unlisted for use in combination with chemotherapy, this risk would need to be mitigated through a written Authority Required listing.
- 7.21 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]
- 7.22 The PBAC considered that if rituximab were PBS-listed in this setting, then any relevant cost-offsets for its substitution should be included in the financial estimates.

- 7.23 Evaluation of a revised economic model structure with appropriate inputs would require a major re-submission.
- 7.24 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

**8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised 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.

**9 Sponsor's Comment**

Roche is disappointed with this outcome for patients with CLL and considers that there is an important place for obinutuzumab in the treatment of this disease. Roche welcomes the Committee's acceptance of the clinical need, positioning, clinical data and of the comparators presented in the submission. Roche looks forward to engaging further with the Committee to address their remaining concerns with the economic model.