5.7 OFATUMUMAB 100 mg/5 mL injection, 5 mL vial, 1 g/50 mL injection, 50 mL vial; Arzerra®; GlaxoSmithKline Australia Pty Ltd.

1 Purpose of application

1.1 The submission sought Section 100 funding (streamlined authority required) of chemotherapy listing for ofatumumab in combination with chlorambucil or bendamustine, for treatment of a patient with CD20 positive, chronic lymphocytic leukaemia (CLL) as first-line therapy for up to 12 treatment cycles of 28 days.

2 Requested listing

2.1 An abridged version of suggestions proposed by the Secretariat to the requested listing are as follows (note – the Secretariat has removed combination treatment with bendamustine from the requested listing as bendamustine is not PBS listed for CLL):

INITIAL

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
OFATUMUMAB				
100 mg/5mL injection vial	3	0	Arzerra®	GK
1000 mg/50mL injection vial	1	5		

CONDITION
Chronic Lymphocytic Leukaemia (CLL)

TREATMENT PHASE
Initial treatment

RESTRICTION
Section 100 (Efficient Funding of Chemotherapy)
Authority required (STREAMLINED)

CLINICAL CRITERIA
The condition must be previously untreated
AND
The treatment must be in combination with chlorambucil
AND
Patient must have CD20 positive chronic lymphocytic leukaemia (CLL)

CONTINUING

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
OFATUMUMAB 1000 mg/50mL injection vial	1	5	Arzerra®	GK

CONDITION
Chronic Lymphocytic Leukaemia (CLL)

TREATMENT PHASE
Continuing treatment

RESTRICTION
Section 100 (Efficient Funding of Chemotherapy)
Authority required (STREAMLINED)

CLINICAL CRITERIA
Patient must have previously been issued with an authority prescription for this drug
AND
The treatment must be in combination with chlorambucil
AND
Patient must have CD20 positive chronic lymphocytic leukaemia (CLL)

2.2 The submission requested listing on the basis of a claim of cost-effectiveness compared with chlorambucil.

2.3 The Pre-Sub-Committee Response's (PSCR, p1) conceded a willingness to include an additional criterion stating that the patient must be 'inappropriate for fludarabine based therapy' based on clinical judgement, if PBAC considered it necessary.

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

3 Background

3.1 The submission was made under TGA/PBAC Parallel Process. A positive TGA Delegate's summary was received on 24 September 2014.

3.2 The Delegate suggested the TGA indication of ofatumumab to be:
"ARZERRA (ofatumumab) is indicated in combination with either chlorambucil or bendamustine for the treatment of patients with chronic lymphocytic leukaemia (CLL) who have not received prior therapy and are inappropriate for fludarabine-based therapy."

3.3 Ofatumumab was previously registered for treatment of patients with B-cell chronic lymphocytic leukaemia (CLL) refractory to fludarabine and alemtuzumab.

3.4 Ofatumumab has not previously been considered by PBAC for this indication. Rituximab plus fludarabine and cyclophosphamide (FC) was recommended for listing by the PBAC on November 2010. In January 2011, the PBAC recommended that the rituximab restriction be adjusted to include combination with chemotherapy rather

than only with FC. While listing did not proceed at that time, the PBAC noted the advice of the Department that discussions with the sponsor of rituximab had recently been held with the aim of progressing this recommendation. Obinutuzumab in combination with chlorambucil for the treatment of previously untreated CD20 positive CLL patients with comorbidities was rejected at the July 2014 meeting. The reason for rejection was that the submission failed to demonstrate that obinutuzumab was cost effective.

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

4 Clinical place for the proposed therapy

4.1 The proposed clinical treatment algorithm placed ofatumumab in combination with chlorambucil or bendamustine as an alternative to chlorambucil therapy for patients with advanced active CLL and who are less fit with relevant co-morbidities.

4.2 The submission placed ofatumumab in combination with chlorambucil or bendamustine as first line therapy for CLL. This is not consistent with either the TGA approved restriction or the proposed clinical treatment algorithm in the submission.

4.3 Retreatment with ofatumumab plus chlorambucil is included in the economic model of the submission, but is not included in the PBS restriction.

5 Comparator

5.1 Chlorambucil monotherapy is used as the main comparator throughout the submission. The Commentary stated that this is the appropriate comparator if the proposed listing is consistent with the proposed TGA indication which states that patients are only considered for ofatumumab therapy if they are inappropriate for fludarabine-based therapy. However, the restriction proposed in the submission allows treatment as a first-line therapy for all previously untreated CLL patients. Chlorambucil plus rituximab may be an appropriate secondary comparator for this indication; this comparison was compiled and presented in the commentary.

5.2 The ESC noted that if the restriction changed as proposed in the PSCR (p1), to include an additional clinical criterion stating that the patient must be inappropriate for fludarabine based therapy, then this is not a key issue.

5.3 The ESC agreed that it is likely that chlorambucil is the primary comparator although there may be some displacement from other treatments including fludarabine plus cyclophosphamide plus rituximab.

5.4 The Commentary had noted that the clinical evidence for bendamustine as a co-therapy is very limited. The PSCR (p1) acknowledged that the clinical evidence for bendamustine as a co-therapy is not comparative.as the OMB115991 trial was not sufficiently mature to allow an assessment of progression free survival.

5.5 If an unrestricted first-line PBS listing is sought, contrary to the proposed indication, fludarabine cyclophosphamide plus rituximab combination therapy (FCR) is the most

prescribed therapy and would be the appropriate comparator.

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 that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on one head-to-head trial comparing ofatumumab plus chlorambucil to chlorambucil (n = 447) and one supplementary single arm study with ofatumumab plus bendamustine (n = 97). An indirect comparison using the ofatumumab plus chlorambucil trial and one trial comparing rituximab plus chlorambucil with chlorambucil (n = 351) was presented in the commentary.

6.4 Details of the trials presented in the submission are provided in the table below.

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial – ofatumumab plus chlorambucil vs. chlorambucil		
OMB110911 (COMPLEMENT-1)	A Phase III, open label, randomized, multicenter trial of Ofatumumab added to Chlorambucil vs. Chlorambucil Monotherapy in previously untreated patients with Chronic Lymphocytic Leukaemia (COMPLEMENT 1). Report Authors: McKeown, A; Carey, J; Gupta, I et al.	Date: Aug 2013 Primary study report number: 2013N163579_01
Supplementary randomised study – ofatumumab plus bendamustine		
OMB115991	A Phase II, Multi-center Study Investigating the Safety and Efficacy of Ofatumumab and Bendamustine Combination in Patients with Untreated or Relapsed Chronic Lymphocytic Leukaemia (CLL). Report Authors: Wright, O; Gorczyca, M; Gupta, I et al.	Date: Aug 2013 Primary study report number: 2013N163233_00
Trial used for indirect comparison – rituximab plus chlorambucil vs. chlorambucil		
CLL11	Goede V, Fischer K, Busch R et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions.	N Eng J Med, March 20, 2014; 370:1101-1110

Source: Table 5, p36 of the submission

6.5 The key features of the direct randomised trial, supplementary study and trial used for the indirect comparison are summarised in the table below.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Ofatumumab + chlorambucil vs. chlorambucil						
COMPLEMENT-1	447	R, MC, OL, 5 years median follow-up: 29 months	Low	Adult patients with diagnosis of CLL, Considered inappropriate for fludarabine based therapy	PFS, OS	Used
Supplementary randomised trial (Ofatumumab + bendamustine)						
OMB115991	97	R, DB, OL, SA, 3 years median follow up: 8.6 months	High	Failed chemo	ORR, PFS, OS,	Not used
Rituximab + chlorambucil vs. chlorambucil						
CLL11 Stage 1a	356	R, OL, MC 3 years median follow-up: 18.7 months	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; SA = single arm; ORR = overall response rate
Source: compiled during the evaluation

The study which included bendamustine co-treatment is a single arm study, which does not provide comparative evidence. The results of this study are not presented below.

Comparative effectiveness

6.6 The table below presents the key results from COMPLEMENT-1.

Key results across the direct randomised trials

Trial ID	Ofatumumab plus chlorambucil n with event/N (%)	Chlorambucil n with event/N (%)	RD (95% CI)	HR (95% CI)
Progression free survival				
COMPLEMENT-1	136/221 (62)	151/226 (67)	[redacted]	**0.57 (0.45, 0.72)**
Overall survival				
COMPLEMENT-1	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 19, p58 & table 3, p5 of the submission and compiled during the evaluation

6.7 A statistically significant improvement in progression free survival was observed for ofatumumab plus chlorambucil compared to chlorambucil treatment (HR: 0.57, 95% CI: 0.45, 0.72), however no statistically significant improvement in overall survival was observed (HR: [redacted] 95% CI: [redacted]).

6.8 Using the naïve indirect comparison between ofatumumab plus chlorambucil and rituximab plus chlorambucil, using chlorambucil monotherapy as the common comparator, there were no differences in progression free survival (HR: 1.3, 95% CI: 0.91 to 1.84) and overall survival (HR: 1.38 95% CI: 0.50, 3.80). There are some

limitations to this indirect comparison. It does not formally adjust or otherwise control for significant differences in key baseline characteristics, dosing regimens or study design and protocol between the COMPLEMENT-1 and CLL11 study populations. Although this naïve indirect comparison provides a broad estimate of the probable difference in PFS between ofatumumab plus chlorambucil compared with rituximab plus chlorambucil combination therapy, the width of the confidence interval around the point estimate HR is likely to be under-estimated as it does not incorporate this between-trial heterogeneity.

6.9 The PSCR (p2) suggested this indirect comparison to be infeasible and of no value due to significant inconsistencies between trials. The PSCR (p2) further considered the naïve comparison conducted by the evaluator did not adjust for differences in the clinical trials (including differences in chlorambucil dose and patient population characteristics including β2 microglobulin) and consequently should not be published.

6.10 The ESC disagreed that an indirect comparison is of no value due to inconsistencies in trials. The ESC considered that the baseline differences, if known, can translate/inform a judgement of the reliability of the estimates and/or further corroborate the sponsor's claim of excessive between-trial heterogeneity. There are various statistical extensions to a naïve indirect comparison that may be appropriate and informative depending upon the availability of patient-level data from the CLL11 trial. Propensity-based methods may enable derivation of comparable sub-groups from the COMPLEMENT-1 and CLL11 trials, at least with regards to those patient and trial characteristics that are common to, and available from, both trials. Such an approach might permit an indirect comparison that has fewer issues of excessive between-trial heterogeneity. Whilst an adjusted indirect comparison would not control for differences in chlorambucil dosing between the trials, an adjusted approach, as a sensitivity analysis, would permit better quantification of the reliability of the naïve indirect comparison. It would also provide, a statistical basis upon which to decide whether between-trial heterogeneity is too excessive to trust the results of an indirect comparison, adjusted or unadjusted.

6.11 The ESC further noted that PBAC did not consider the chlorambucil dosing an issue for the obinutuzumab and rituximab trials. Therefore this may not have a huge impact on the indirect comparison.

6.12 The ESC considered the evidence suggests that ofatumumab + chlorambucil is unlikely to be superior to rituximab + chlorambucil.

Comparative harms

6.13 The table below presents the key adverse events from COMPLEMENT-1.

Summary of key adverse events in COMPLEMENT-1

Adverse Event	Ofatumumab plus chlorambucil n (%) N=217	Chlorambucil n (%) N=227	RD (95% CI)
Any adverse event	[redacted]	[redacted]	[redacted]
AEs leading to dose interruption	[redacted]	[redacted]	[redacted]
Neutropenia	59 (27)	41 (18)	**0.09 (0.03, 0.15)**
Thrombocytopenia	30 (14)	59 (26)	**-0.12 (-0.17, -0.07)**
Infusion related reaction	20 (9)	0	**0.09 (0.05, 0.13)**
Respiratory failure	5 (2)	1 (<1)	**0.02 (0.00, 0.04)**
Tumour lysis syndrome	4 (2)	0	**0.02 (0, 0.04)**

Source: Tables 25-26, pp67-68 of the submission and compiled during the evaluation.
RD = risk difference; AE = adverse event; CI = confidence interval

6.14 In COMPLEMENT-1, ofatumumab plus chlorambucil resulted in an inferior safety profile relative to chlorambucil. The adverse events that occurred more often in the ofatumumab arm were infusion-related reaction, neutropenia, respiratory failure and tumour lysis syndrome. The chlorambucil monotherapy arm had more episodes of thrombocytopenia.

6.15 In the indirect comparison, there were only slight differences in key adverse events, with ofatumumab plus chlorambucil having increased infusion related reactions (RD: 0.05, 95% CI: 0 to 0.1) and reduced thrombocytopenia compared to rituximab plus chlorambucil (RD: -0.11, 95% CI: -0.18, -0.4). There are some limitations to this indirect comparison.

Benefits/harms

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

Summary of comparative benefits and harms for ofatumumab plus chlorambucil and chlorambucil

Benefits						
PFS/OS: Trial COMPLEMENT-1, median follow-up 29 months						
	ofatumumab plus chlorambucil	**Chlorambucil**	**Absolute Difference**	**HR (95% CI)**		
PFS, n/N	136/221	151/226	-	**0.57 (0.45, 0.72)**		
Median PFS; mths (95% CI)	22.4 (19.0, 25.2)	13.1 (10.6, 13.8)	9.3	-		
OS, n/N	[redacted]	[redacted]		[redacted]		
Harms						
	O + Chl	**Chl**	**RR (95% CI)**	**Event rate/100 patients***		**RD (95% CI)**
				O + Chl	**Chl**	
COMPLEMENT-1, median follow-up 29 months						
Infusion related reaction	20/217	0/227	**-**	9	0	**0.09 (0.05, 0.13)**
Neutropenia	59/217	41/227	**1.51 (1.06, 2.14)**	27	18	**0.09 (0.03, 0.15)**
Thrombocytopenia	30/217	59/227	**0.53 (0.36, 0.79)**	14	26	**-0.12 (-0.17, -0.07)**

* Median duration of follow-up = 29 months.
O + Chl = ofatumumab plus chlorambucil; Chl = chlorambucil; RD = risk difference; RR = relative risk; HR = hazard ratio; **bold**

= statistically significant.
Source: Table 19, p58, table 21, p61 and tables 25-26, pp67-68 of the submission and compiled during the evaluation

6.17 On the basis of direct evidence presented by the submission, the comparison of ofatumumab plus chlorambucil and chlorambucil monotherapy with a median duration of follow-up of 29 months resulted in:

- Approximately 9.3 months difference in progression free survival.

No difference was observed in overall survival, which may be due to the limited follow-up of the trial for patients with indolent CLL. This is inconsistent with the economic model, which includes a survival gain.

On the basis of direct evidence presented by the submission, for every 100 patients treated with ofatumumab plus chlorambucil, in comparison to chlorambucil monotherapy, over a 29 month median duration of follow-up:

- Approximately 9 additional infusion-related reactions;
- Approximately 9 additional neutropenia;
- Approximately 12 less thrombocytopenia.

6.18 A summary of the comparative benefits and harms for ofatumumab plus chlorambucil versus rituximab plus chlorambucil, using an indirect comparison with chlorambucil as common comparator is presented in the table below.

[indirect comparison] Summary of comparative benefits and harms for ofatumumab plus chlorambucil and rituximab plus chlorambucil

Benefits								
Median progression free survival (months) **Median follow-up COMPLEMENT-1: 29 months, CLL-11: 18.7 months**								
	O + Chl	**Chl**	**R + Chl**	**Absolute Difference**			**HR (95% CI)**	
COMPLEMENT-1	22.4	13.1		**9.3 months**			**0.57 (0.45, 0.72)**	
CLL-11		11.1	16.3	**5.2 months**			**0.44 (0.34, 0.57)**	
Indirect Comparison							1.3 (0.91, 1.84)	
Overall-survival - number of deaths								
	O + Chl	**Chl**	**R + Chl**	**HR (95% CI)**	**Event rate/100 patients***			**RD (95% CI)**
					O + Chl	**Chl**	**R + Chl**	
COMPLEMENT-1	33/221	40/227		[redacted]	[redacted]	[redacted]		[redacted]
CLL-11		24/118	35/233	[redacted]		[redacted]	[redacted]	[redacted]
Indirect Comparison				[redacted]				[redacted]
Harms								
Any Adverse event								
	O + Chl	**Chl**	**R + Chl**	**RR (95% CI)**	**Event rate/100 patients***			**RD (95% CI)**
					O + Chl	**Chl**	**R + Chl**	
COMPLEMENT-1	206/217	203/227	-	**1.06 (1.0, 1.1)**	95	89		**0.06 (0.01, 0.11)**
CLL-11		58/116	125/225	1.11 (0.9, 1.4)	-	50	56	0.06 (-0.06, 0.17)
Indirect comparison:					-			0.0 (-0.13, 0.13)
Infusion-related reactions								
COMPLEMENT-1	20/217	0/227	-	NC	9	0		**0.09 (0.05, 0.13)**
CLL-11		0/116	9/225	NC	-	0	4	**0.04 (0.01, 0.07)**
Indirect comparison:					-			**0.05 (0.0, 0.1)**

* Median duration of follow-up: COMPLEMENT-1 = 29 months; CLL11 = 18.7 months.
RD = risk difference; RR = risk ratio; O + Chl = ofatumumab plus chlorambucil; Chl = chlorambucil; R + Chl = rituximab plus chlorambucil; NC = not calculated; **bold** = statistically significant. Source: Compiled during the evaluation, Tables 25-26, pp67-

68 and Table 126, p226 of the submission and Goede et al. 2014 p.1105.

6.19 Based on an indirect comparison using chlorambucil as the common comparator, ofatumumab + chlorambucil is unlikely to be superior to rituximab + chlorambucil in the treatment of previously untreated patients with CLL. For CLL, the outcomes assessed were progression free survival and overall survival.

On the basis of indirect evidence compiled during the evaluation, for every 100 patients treated with ofatumumab plus chlorambucil, in comparison to rituximab plus chlorambucil, over a 29 month median duration of follow-up compared to a 19 month follow up:

- Approximately 5 additional infusion-related reactions;
- No important overall differences in adverse events.

Clinical claim

6.20 The submission describes ofatumumab plus chlorambucil or bendamustine as superior in terms of comparative effectiveness compared to chlorambucil monotherapy and an acceptable safety profile. The claim of superior efficacy of ofatumumab plus chlorambucil is supported by the evidence; the claim of acceptable safety profile was accepted by ESC.

6.21 The claim of superior efficacy and non-inferiority in terms of safety of ofatumumab plus bendamustine compared to chlorambucil is not supported by clinical evidence. The ESC noted the PSCR's clarification (p1) that a superiority claim is not sought as the comparative evidence is limited.

6.22 The submission does not make a claim with regards to rituximab plus chlorambucil, as it considers that it is inappropriate to compare the two trials in an indirect comparison. Based on the clinical evidence provided, ESC considered it is unlikely ofatumumab plus chlorambucil is superior to rituximab plus chlorambucil, noting the limitations of the indirect comparison due to differences in patient characteristics, duration of follow-up and the large confidence intervals.

Economic analysis

6.23 The type of economic evaluation presented is a cost-utility analysis for the comparison with chlorambucil monotherapy.

Summary of model structure and rationale

Component	Summary
Time horizon	15 years in the model base case versus 2.4 years in the trial
Outcomes	LYG, QALYs and costs
Methods used to generate results	Cohort expected value analysis, extrapolated trial data and Markov model
Health states	Complete response, partial response, stable disease, best supportive care, second line treatment, third line treatment, fourth line treatment.
Cycle length	3 months
Transition probabilities	PFS from COMPLEMENT-1 Overall survival and time to progression (for further lines of therapy) were extrapolated from numerous sources

Source: compiled during the evaluation

6.24 The table below presents the key drivers for the economic model.

Key drivers of the model

Description	Method/Value	Impact
Time horizon	15 years; assumed from 29 month median trial follow up	High, favours ofatumumab
Overall survival	There was no statistical difference in COMPLEMENT-1; the detected HR of [redacted] is used and applied to data from Rai (2009) to extrapolate long term survival	Moderate, favours ofatumumab
Subsequent lines of therapy	Subsequent lines of therapy are based on data from various sources and include fludarabine; which may not reflect clinical practice	Unclear
Progression to next therapy	Next treatment was assumed to occur immediately after progression, this does not reflect clinical practice as treatment is delayed in COMPLEMENT-1	Unclear, favours ofatumumab

Source: compiled during the evaluation

Results of the economic evaluation

Step and component	Ofatumumab plus chlorambucil	Chlorambucil	Increment
Costs	[redacted]	[redacted]	[redacted]
QALY	[redacted]	[redacted]	[redacted]
Incremental cost/extra QALY gained			[redacted]

Source: Table 93 p166 of the submission

6.25 The economic evaluation results in ICERs of $45,000-$75,000 per QALY for ofatumumab plus chlorambucil vs. chlorambucil. The ICER is not reliable due to:

- The use of subgroups for progression free survival based on best response results in illogical results for chlorambucil patients who achieved a complete response (CR). That is, the model predicts that a patient treated with chlorambucil will have a longer PFS ([redacted] months) when he or she has a partial response (PR) compared to a complete response ([redacted] months). The PSCR (p2, 3) counters this with the suggestion that that only small numbers (1.3%) of chlorambucil only patients had a complete response (CR) so their PFS has a small influence on the results of the model. The PSCR further argues that parametric survival analyses were included in the economic model to allow exploration of this parameter. These functions provided logical outcomes in that patients treated with chlorambucil only or ofatumumab plus chlorambucil who achieve CR have longer PFS than patients who achieve PR. The ESC considered that the model lacks face validity if the patients with a CR have less overall survival than those with a PR.
- The extrapolation of overall survival beyond the trial duration results in differences in overall survival between the two comparisons, with lower overall survival compared to registry data in the US or Australia. The PSCR (p3) argues that a time horizon beyond 10 years is valid because approximately [redacted]% of patients in the ofatumumab plus chlorambucil are still alive at 10 years versus [redacted]% at 15 years. The ESC considered this confirmed a lack of validity with the modelled extrapolation of survival. Australian data indicate patients not on fludarabine based regimens have an average age of 73.5 years, so using the life expectancy argument in the PSCR (p3) would suggest 10 years is a generous time horizon. The PSCR (p3) stated it could not access SEER data or Australian data. The ESC noted that they are available at: the SEER data at http://seer.cancer.gov/faststats/ and the Australian cancer registry data through

the Australian Institute of Health and Welfare website at http://www.aihw.gov.au/publication-detail/?id=10737422720.

- Inappropriate second line therapies are included in the model, i.e. fludarabine is considered inappropriate for the patients included in the economic model, however further lines of treatment consist of fludarabine (approximately [redacted]%). The PSCR (p4) argued that second line therapies included in the economic model are appropriate as they were based on Australian treatment practices and reflect a different risk/benefit assessment after the initial therapy.

6.26 The submission presents various univariate sensitivity analyses and probabilistic sensitivity analyses, and additional sensitivity analyses were performed during evaluation.

Results of univariate and multivariate sensitivity analyses

	Δ costs	Δ QALY	ICER
Base case	[redacted]	[redacted]	[redacted]
Univariate analyses			
Time horizon (base case 15 year)			
10 years	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]
Utility weights from COMPLEMENT-1[a]	[redacted]	[redacted]	[redacted]
OS (base case: HR 0.91, extrapolation using Rai (2009) adjustment, no conversion of efficacy)			
Tapering of HR after trial period (5 years) to HR = 1.0 at 10 year	[redacted]	[redacted]	[redacted]
OS HR 1.0 after trial period (5 year)	[redacted]	[redacted]	[redacted]
OS HR 1.0 after trial period (29 months = median follow up)	[redacted]	[redacted]	[redacted]
OS from individual treatment arms, HR 1.0 after trial period	[redacted]	[redacted]	[redacted]
HR Lower CI OS from trial (0.57) for duration of model	[redacted]	[redacted]	[redacted]
HR Upper CI OS from trial (1.43) for duration of model	[redacted]	[redacted]	[redacted]
% chlorambucil patients progressing to 3rd line = 45% (base case 50%)	[redacted]	[redacted]	[redacted]
Fludarabine based therapy removed for second line therapy [b]	[redacted]	[redacted]	[redacted]
Number of cycles = 9 (base case 6.4) [c]	[redacted]	[redacted]	[redacted]
Multivariate analyses			
Time horizon = 10 year, HR = 1 after trial follow-up	[redacted]	[redacted]	[redacted]
Time horizon = 10 years, HR = 1 after trial follow-up; number of cycles = 9 [c]	[redacted]	[redacted]	[redacted]

Source: Table 94-95, p167of the submission and compiled during evaluation.

OS = overall survival; HR = hazard ratio; Δ = incremental; QALY= quality adjusted life years; ICER = incremental cost-effectiveness ratio. KM = Kaplan Meier: PFS = progression free survival

[a] Disutilities: Complete Response = [redacted]; Partial Response = [redacted]; Stable Disease = [redacted]; Progression & Re-treatment, Progression and subsequent lines of therapy and Progression & BSC = 0

[b] Chlorambucil = [redacted]; Rituximab = [redacted]; Rituximab + Chlorambucil = [redacted]; Other = [redacted].

[c] Based on modifying costs of drug usage and administration, utilities assumed not to be affected.

6.27 The sensitivity analyses conducted by the submission resulted in an ICER range from $45,000-$75,000/QALY to $45,000-$75,000/QALY gained. Analyses performed during evaluation, resulted in higher ICERs, with the key drivers being the extrapolation assumptions for overall survival, time horizon, number of treatment cycles, and subsequent lines of therapy.

6.28 Table 3 in the PSCR offers a range of sensitivity analyses on the survival function resulting in a range of ICERs between $45,000-$75,000/QALY to $75,000-$105,000/QALY.

Drug cost/patient/treatment:

6.29 Estimated [redacted] assuming [redacted] 100 mg vials and [redacted] 1000 mg vials, equating to [redacted] cycles per patient and [redacted]% of scripts are dispensed in a public hospital.

Estimated PBS usage & financial implications

6.30 This submission was not considered by DUSC.

6.31 The submission takes an epidemiological approach to forecast the uptake of ofatumumab over a five year period using data from, AIHW (2014), The Ipsos Oncology Monitor (2014), COMPLEMENT-1, Australian clinicians 2013, Canadian clinicians 2013 & ABS (2012). The financial estimates are based on ofatumumab plus chlorambucil being used in patients who are not receiving fludarabine based therapies.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100 mg Scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1000 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated total net cost					
Net cost to PBS/RPBS/MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Electronic Attachment 2 - Section E Workbook.xlsm

The redacted table shows that the number of patients estimated to receive treatment with ofatumumab is less than 10,000 per year. The estimated net cost to the PBS/MBS/RPBS is less than $10 million per year in the first 2 years of listing, increasing to $10-20 million for years 3-5.

6.32 The cost to Government may be higher or lower due to:

- Estimated number of patients treated with ofatumumab;
- Different uptake rates;
- Comparison with only chlorambucil monotherapy used, whereas rituximab plus chlorambucil or rituximab monotherapy are also likely to be replaced;
- The use of ofatumumab in patients with fewer comorbidities;
- Use outside of PBS restriction, e.g. retreatment post progression after two years or as a second-line treatment after failure of other first line treatments.

6.33 The submission presents sensitivity analyses around prevalence, uptake and number of ofatumumab cycles, with an increase in the number of cycles per person to nine having the largest impact on the overall cost to the PBS/RPBS ($60-100 million over five years). The submission does not test the use of ofatumumab as a second-line treatment after failure of either ofatumumab or other first line treatment.

6.34 The PSCR (p4) stated that other therapies are not PBS listed for this population, so there is variable funding and patient access. When the substitution of these therapies is included in the analysis, the PSCR estimates there is an additional cost offset of approximately $10-$20 million to the PBS/RPBS over the first 5 years of listing.

Financial Management – Risk Sharing Arrangements

6.35 The Sponsor indicated willingness to undertake a mutually agreeable risk sharing agreement to address concerns relating to uncertainty in utilisation (PSCR, p4).

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of ofatumumab in combination with chlorambucil for the treatment of chronic lymphocytic leukaemia (CLL). The recommendation was formed on the basis of a cost-minimisation with rituximab. The PBAC reaffirmed its recommendation originally made in January 2011 (out-of-session) and confirmed in July 2014 to list rituximab for the treatment of CD20 positive CLL in combination with chemotherapy. The PBAC further advised that the listing of ofatumumab should be at a price no higher than that deemed appropriate for rituximab.

7.2 In making this recommendation, the PBAC noted the choice of chlorambucil monotherapy as the main comparator outlined in the submission. However, the PBAC considered that the drug most likely to be replaced in clinical practice, particularly by the time ofatumumab may be PBS listed, will be rituximab. PBAC considered chlorambucil was an appropriate secondary comparator, noting the key clinical trial COMPLEMENT-1 directly compares the combination of ofatumumab and chlorambucil against chlorambucil.

7.3 In the consideration of the evidence used for the indirect comparison with rituximab, 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.

7.4 The PBAC noted the Sponsor's argument in the PSCR (p2) that comparability across the COMPLEMENT-1 and CLL11 studies to inform the indirect comparison of ofatumumab and rituximab was infeasible due to the lack of adjustment for the differences in the clinical trials, including chlorambucil dose. The Committee disagreed with the Sponsor and considered that the latter may not have a significant impact on the indirect comparison recalling previous decisions in both obinutuzumab (July 2014 PBAC) and rituximab (November 2010) trials where PBAC did not consider variations in chlorambucil dosing to be a significant issue.

7.5 Overall, the committee noted the incomplete and less than rigorous comparison of ofatumumab with rituximab. However, in the absence of direct trial data between ofatumumab and rituximab and given the high clinical need in the patient group, the PBAC accepted this evidence as adequate to support non-inferiority to rituximab.

7.6 The Committee agreed that dose equivalence of ofatumumab to rituximab is to be defined based on per course of treatment and calculated based on the surface area of an average patient. From the Product Information, rituximab is administered intravenously at a dose of 375 mg/m^2 of body surface area on day 1 of cycle 1 and 500 mg /m^2 on day 1 of cycles 2-6.

7.7 The PBAC recommended ofatumumab, an antineoplastic agent, be exempt from the Safety Net 20 Day Rule.

7.8 The PBAC recommended ofatumumab to be unsuitable for inclusion on the list of PBS medicines for prescribing by nurse practitioners or midwives.

7.9 Under Section 101 (3BA) of the National Health Act, the PBAC recommended that ofatumumab and rituximab should be treated as interchangeable on an individual patient basis for this indication only.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

INITIAL (1)

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
OFATUMUMAB 100 mg/5mL injection vial	3	0	Arzerra®	GK

CONDITION
Chronic Lymphocytic Leukaemia (CLL)

TREATMENT PHASE
Initial treatment

RESTRICTION
Section 100 (Efficient Funding of Chemotherapy)
Authority required (STREAMLINED)

CLINICAL CRITERIA
The condition must be 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 be inappropriate for fludarabine based therapy

ADMINISTRATIVE ADVICE

An initial dose of 1300 mg of PBS-subsidised ofatumumab must be made up of 3 vials of 100 mg and 1 vial of 1000 mg

ADMINISTRATIVE ADVICE
No increase in the maximum quantity or number of units may be authorised.

INITIAL (2)

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
OFATUMUMAB 1000 mg/50mL injection vial	1	5	Arzerra®	GK

CONDITION
Chronic Lymphocytic Leukaemia (CLL)

TREATMENT PHASE
Initial treatment

RESTRICTION
Section 100 (Efficient Funding of Chemotherapy)
Authority required (STREAMLINED)

CLINICAL CRITERIA
The condition must be 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 be inappropriate for fludarabine based therapy

ADMINISTRATIVE ADVICE
An initial dose of 1300 mg of PBS-subsidised ofatumumab must be made up of 3 vials of 100 mg and 1 vial of 1000 mg.

ADMINISTRATIVE ADVICE
No increase in the maximum quantity or number of units may be authorised.

CONTINUING

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
OFATUMUMAB 1000 mg/50mL injection vial	1	5	Arzerra®	GK

CONDITION
Chronic Lymphocytic Leukaemia (CLL)

TREATMENT PHASE
Continuing treatment

RESTRICTION
Section 100 (Efficient Funding of Chemotherapy)
Authority required (STREAMLINED)

CLINICAL CRITERIA
The condition must be CD20 positive chronic lymphocytic leukaemia (CLL)
AND
Patient must have previously been issued with an authority prescription for this drug
AND
Patient must not have progressive disease
AND
Patient must be inappropriate for fludarabine based therapy
AND
The treatment must be in combination with chlorambucil

ADMINISTRATIVE ADVICE
No increase in the maximum quantity or number of units may be authorised.

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

GlaxoSmithKline welcomes the PBAC's recommendation to list Arzerra on the PBS for the treatment of chronic lymphocytic leukaemia.