6.05 IBRUTINIB, Capsule 140 mg, Imbruvica®, Janssen-Cilag Pty Ltd

1 Purpose of application

1.1 Section 85 Authority Required (telephone) listing for ibrutinib for first-line treatment of chronic lymphocytic leukaemia (CLL) or small lymphocytic leukaemia (SLL) in unfit patients, i.e. those unsuitable for treatment with a fludarabine-based chemoimmunotherapy. The requested listing has not been previously considered by PBAC.

1.2 The submission sought listing on the basis of a cost utility analysis compared to rituximab, obinutuzumab and ofatumumab, with each comparator in combination with chlorambucil.

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

Component	Description
Population	Previously untreated unfit patients with CLL/SLL.
Intervention	Ibrutinib - 3×140mg capsules taken orally once daily. Treatment continues until disease progression or until ibrutinib is no longer tolerated by the patient.
Comparator	Rituximab administered intravenously 375mg/m^2 dose on Day 1 of first 28 day cycle and 500mg/m^2 on day 1 of each subsequent 28 day cycle + chlorambucil 10mg/m^2/day for 7 days of each 28 day cycle administered orally. Maximum treatment is 6 cycles Obinutuzumab administered intravenously 100mg day 1, 900mg day 2 and 1000mg on days 8 and 15 in the first 28 day cycle and subsequent cycles 1000mg once per cycle + chlorambucil 10mg/m^2/day for 7 days of each 28 day cycle administered orally. Maximum treatment is 6 cycles Ofatumumab administered intravenously 300mg on day 1 (3 x 100mg injections) and 1000mg on day 8 + chlorambucil 10mg/m^2/day for 7 days of each 28 day cycle administered orally. Maximum treatment is 12 cycles.
Outcomes	Progression-free survival; overall survival.
Clinical claim	Ibrutinib has superior comparative effectiveness compared to obinutuzumab+chlorambucil (obi+chl), rituximab+chlorambucil (ritux+chl) and ofatumumab+chlorambucil (ofa+chl). With a numerically similar incidence of adverse events but a different safety profile ibrutinib is non-inferior to the comparators. The claim of superiority for ibrutinib was not strongly supported, given lack of statistically significant differences for PFS and OS compared to obinutuzumab+chlorambucil (see Section 6 below).

Source: Section A, p3-6 of Section A of the submission; Section A.3, p13 of Section A of the submission; Section Bii.5.1, p40-42 of Section Bii of the submission; Section Bii.5.2, p44-45 of Section Bii of the submission; Section Bii.8, p103 of Section Bii of the submission; Excel workbook Section E.xlsx.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
IBRUTINIB			$8,782.81[a] (published)	
Capsules 140mg, 90	1	5	$[redacted][a] (effective)	Imbruvica® JC

Category / Program:	Section 85
PBS Indication:	Chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL)
Treatment phase:	Initial and continuing
Restriction:	Section 85 Authority required (telephone)
Treatment criteria:	Previously untreated
Clinical criteria:	Patient must be previously untreated AND The treatment must be as monotherapy AND Patient must be inappropriate for fludarabine-based therapy AND Patient must have a WHO performance status of 2 or less
Prescriber Instructions	Patient must not receive PBS-subsidised ibrutinib if progressive disease develops while on PBS-subsidised ibrutinib[b]

[a] The requested prices have been updated to include the Administration, Handling and Infrastructure (AHI) fee ($72.43) and dispensing fee ($7.15) that are current as of 1 July 2017.

[b] While the submission included this criteria regarding development of progressive disease as part of its requested clinical criteria, for the recommended PBS restriction for ibrutinib for relapsed/refractory CLL/SLL this criteria was moved to 'Prescriber instructions' so the same has been done here.

Source: Table A.1, p7 and Table A.3, p10 of Section A of the submission.

2.1 The ESC noted that there is no definition of progressive disease in the proposed restriction. The full iwCLL 2008 criteria for assessing progressive disease while on ibrutinib treatment may be misleading as patients on this class of drug often demonstrate an increased lymphocytosis despite improvement in nodal and bone marrow disease, which may persist for several months. The PBAC considered progressive disease during or after therapy characterised by at least one iwCLL criteria, as per the RESONATE-2 trial protocol, was appropriate.

2.2 While the requested restriction specifies that patients must be unfit for fludarabine-based therapy, criteria were not proposed which detail how 'unfit' is defined. The restriction recommended by the PBAC for use of ibrutinib in relapsed/refractory CLL/SLL patients unfit for treatment with fludarabine-based therapy provided a detailed definition of when a patient would be considered unsuitable for treatment with a purine analogue. The PBAC considered a similar addition to the restriction in previously untreated patients would be appropriate; see suggested prescriber instruction below.

Prescriber instruction:	A patient is considered unsuitable for treatment with a purine analogue as demonstrated by at least one of the following: a. Age ≥ 70 years b. Age ≥ 65 years and the presence of comorbidities (Cumulative Illness Rating Scale ≥ 6 or creatinine clearance <70 mL/min) that might place the patient at an unacceptable risk for treatment-related toxicity with purine analogue-based therapy c. History of autoimmune thrombocytopenia d. 17p deletion

2.3 The submission requested a special pricing arrangement and stated that details of the arrangement would be captured in a Deed of Agreement.

2.4 The requested price is the same as the recommended effective DPMQ per month for ibrutinib for the relapsed or refractory CLL/SLL indication, which was approved for listing on the PBS by the PBAC in January 2017. However, the PBAC's recommendation for listing of Ibrutinib in relapsed/refractory CLL/SLL recommendation was based on, among other matters, its assessment, that the cost-effectiveness of ibrutinib would be acceptable at the prices proposed in the sponsor's submission dated 23 January 2017, and if the measures cited in the sponsor's submission dated 23 January 2017 were implemented to contain risks associated with the cost of ibrutinib to the PBS. By not taking those factors into account, the requested price in this submission for the first-line treatment of CLL is higher than the price at which the PBAC considered ibrutinib to be cost-effective in the relapsed/refractory setting.

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

3 Background

Registration and PBS status

3.1 TGA status: Ibrutinib was recommended for registration for CLL/SLL by the TGA on 20 April 2015 and in November 2016 a new indication for Waldenstrom's macroglobulinemia (WM) was added and the CLL/SLL indication modified. The current TGA indications are as follows:

- Patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.
- Adult patients with CLL/SLL who have received at least one prior therapy or adult patients with previously untreated CLL/SLL.
- Patients with CLL/SLL with deletion 17p.
- Adult patients with WM who have received at least one prior therapy, or in first-line treatment for patients unsuitable for combination chemo-immunotherapy.

3.2 Ibrutinib received a positive recommendation at the January 2017 meeting of the PBAC for the treatment of patients with relapsed or refractory CLL/SLL who are unsuitable for treatment with fludarabine, cyclophosphamide and rituximab (FCR).

Agents already PBS-listed

3.3 Rituximab in combination with non-fludarabine and cyclophosphamide (FC) chemotherapy received a positive PBAC recommendation for CD20 positive CLL in January 2011 (out-of-session, following the November 2010 consideration).

3.4 Ofatumumab in combination with chlorambucil received a positive PBAC recommendation for CLL, in November 2014, at a price no higher than that deemed appropriate for rituximab.

3.5 Obinutuzumab in combination with chlorambucil received a positive PBAC recommendation for CLL in March 2015, on the basis that the combination therapy provided, for some patients, a significant improvement in efficacy over rituximab plus chlorambucil, and chlorambucil monotherapy.

4 Population and disease

4.1 CLL is a B-cell malignancy that presents with peripheral blood involvement while SLL, also a B-cell malignancy and considered to be the same entity, presents with lymph tissue involvement. CLL and SLL primarily affect older persons who often have co-existing conditions. The requested PBS listing is for the treatment of unfit patients, specifically those who cannot tolerate fludarabine-based treatment, who are generally older individuals with co-morbidities.

4.2 The submission states that treatment initiation does not always occur at diagnosis, and the natural history of the disease is one of repeated relapse. The submission adds that the burden of disease is high and is impacted by the presence of major co-morbidities associated with advanced age. In particular, patients with CLL/SLL have a high risk of morbidity and mortality from disease-related infections and in more advanced stages of disease neutropenia due to bone marrow infiltration and/or cytotoxic therapy may also contribute to the increased risk of infection-related morbidity and mortality. The submission also notes negative impacts on patients' quality of life as a result of disease-related symptoms, treatment-related adverse events and the psychological, socioeconomic and functional effects of living with the disease.

4.3 The requested listing is for first-line treatment. The ESC noted the submission's claim that first-line ibrutinib will reduce the need for second-line treatment due to its superior efficacy, and first-line ibrutinib would offset the use of ibrutinib in the relapsed/refractory setting. The economic model assumed ibrutinib is the only treatment used in the second-line setting however there are a number of treatment options for relapsed/refractory patients and it is unlikely that ibrutinib would be used in 100% of relapsed/refractory patients.

5 Comparator

5.1 The submission nominated chlorambucil used in combination with an anti-CD20 monoclonal antibody, either rituximab, obinutuzumab or ofatumumab as the main comparator. The submission cited the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN), which

recommend chlorambucil-based immunochemotherapy regimens (eg chlorambucil in combination with obinutuzumab (obi+chl), ofatumumab (ofa+chl) or rituximab (ritux+chl)) for patients who cannot tolerate treatment with FCR. The submission stated that a blended comparator to estimate the incremental cost-effectiveness of ibrutinib is the most appropriate comparator and most informative for decision making since the recent PBS listing dates of the comparators mean there is limited data to inform which specific immunochemotherapy regimen is the preferred treatment for patients who cannot tolerate FCR. The ESC advised that in academic centres obi+chl is now the preferred treatment option, as the most effective subsidised therapy.

5.2 The submission's choice of a blended comparator does not reflect the efficacy conclusions drawn by the PBAC in its considerations of rituximab, ofatumumab and obinutuzumab. The March 2015 Public Summary Document (PSD) for obinutuzumab states that "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" (paragraph 7.2). With ofatumumab being recommended on a cost-minimisation basis with rituximab and the PBAC accepting the available evidence to support non-inferiority of ofatumumab and rituximab (paragraph 7.5 of the November 2014 ofatumumab PSD), it would be reasonable to conclude that the PBS listing of these agents indicates superior efficacy for obinutuzumab. The Pre-Sub-Committee Response (PSCR) (pp1-2) argued that given obi+chl did not reach statistically significant improvements in OS vs ritux+chl in the March 2015 PBAC consideration, but the indirect comparison of ibrutinib vs ritux+chl did show a significant improvement, it is reasonable to conclude that survival following treatment with ibrutinib is statistically and clinically superior to obi+chl. The ESC noted the evidence of obi+chl superiority vs ritux+chl was based on a direct RCT which demonstrated statistically significant improvements in PFS, and approached statistical significance in OS HR=0.70 (0.47, 1.02). The ibrutinib claims are based on indirect comparisons and are not sufficient evidence to support ibrutinib being superior to obi+chl.

5.3 PBS data of current treatments for first-line CLL in unfit patients demonstrated uptake of obi + chl was increasing (as seen in Figures 1 and 2 below), but ritux+chl was currently the more common treatment. Without robust evidence to justify superiority of ibrutinib vs obi+chl, the ESC considered either non-inferiority to obi+chl or superiority of ibrutinib vs ritux+chl may be the most relevant comparisons for assessing clinical and cost-effectiveness. The PBAC agreed with the ESC.

Figure 1: Number of patient initiations for each treatment (PBS script analysis)

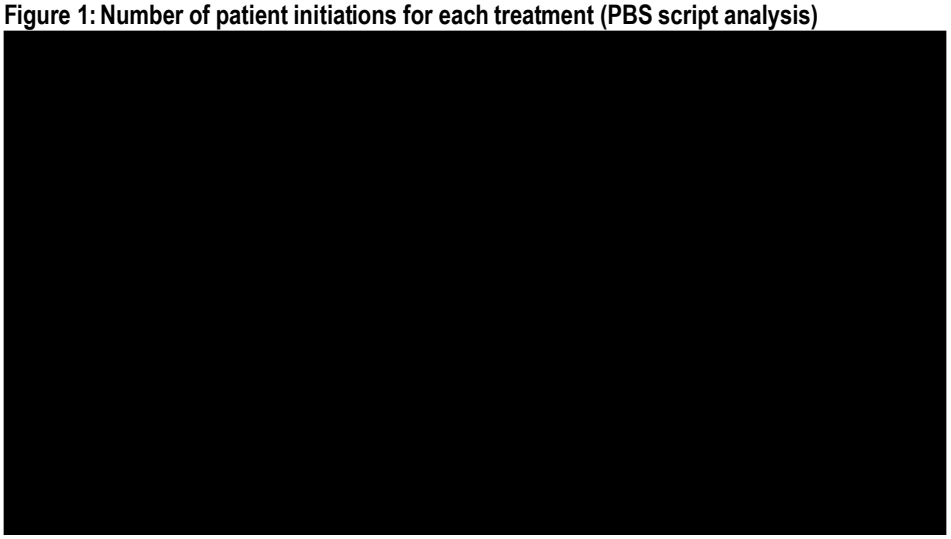


Figure 2: Percentage of patient initiations for each treatment

Source: Figures 1 and 2 of the Pre-sub-committee response (PSCR), p5

5.4 The ICER for ibrutinib versus obi+chl is approximately 20% higher ($75,000 – $105,000) compared with the ICER for ibrutinib versus the blended comparator ($75,000 – $105,000; see Economic analysis below). The blended comparator is not a conservative selection, and appears to favour ibrutinib in regard to estimated cost-effectiveness.

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 (4) and health care professionals (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with ibrutinib including

improved quality of life, and better and more durable responses for patients with deletion 17p/p53 mutation where FCR would be ineffective and toxic.

Clinical trials

6.3 The submission is based on indirect comparisons of ibrutinib to rituximab, obinutuzumab and ofatumumab, the latter three in combination with chlorambucil, with the common reference being chlorambucil monotherapy. The trials used for the indirect comparisons are as follows:

- Ibrutinib: RESONATE-2, a randomised, open-label trial comparing ibrutinib to chlorambucil in patients ≥65 years of age who are considered unfit to receive fludarabine therapy (N=269).
- Rituximab and obinutuzumab: CLL11, a randomised, open-label trial three-arm trial comparing ritux+chl, obi+chl and chl monotherapy in patients where treatment with a fludarabine-based therapy was considered inappropriate (N=589).
- Ofatumumab: COMPLEMENT-1, a randomised, open-label trial comparing ofa+chl to chl monotherapy in patients for whom fludarabine-based regimens were considered inappropriate (N=447).

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

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Trials included in the indirect comparisons		
RESONATE-2	A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor PCI-32765 versus Chlorambucil in Patients 65 Years or Older with Treatment-naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma	August 2015
	Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia	New England Journal of Medicine 2015; 373:2425-2437
CLL11	An Open-label, Multi-center, Three Arm Randomized Study to Investigate the Safety and Efficacy on Progression-free Survival of RO5072759 + Chlorambucil (GClb) Compared to Rituximab + Chlorambucil (RClb) or Chlorambucil (Clb) Alone in Previously Untreated CLL Patients with Comorbidities.	Date not provided.
	Goede V, Fischer K, et al[a]. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions.	New England Journal of Medicine 2014; 370(12): 1101-1110.
	Goede V, Fischer K, et al. Obinutuzumab as frontline treatment of chronic lymphocytic leukemia: updated results of the CLL11 study.	Leukemia 2015; 29:1602-1604.
COMPLEMENT-1	A phase III, open label, randomised, multicenter trial of Ofatumumab added to Chlorambucil versus Chlorambucil Monotherapy in previously untreated patients with Chronic Lymphocytic Leukaemia	August 2013
	Hillmen P, Robak T, Janssens A, et al. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial.	The Lancet 2015; 385(9980): 1873-1883.
	Hillmen P, Robak T, Janssens A, et al. Health-related quality of life and patient-reported outcomes of ofatumumab plus chlorambucil versus chlorambucil monotherapy in the COMPLEMENT 1 trial of patients with previously untreated CLL.	Acta Oncologica 2016; 55(9-10): 1115-1120.
	Frustaci AM, Tedeschi A, et al. Ofatumumab plus chlorambucil as a first-line therapy in less fit patients with chronic lymphocytic leukemia: analysis of COMPLEMENT1 and other monoclonal antibodies association data.	Ther Adv in Hematol 2016; 7(4): 222-230.

[a] The submission also lists a trial protocol and supplementary appendix with the same citation as this paper.
Source: Table B11.7, p11-13 of Section Bii of the submission.

6.5 The key features of the randomised trials used in the indirect comparisons are summarised in the table below.

Table 3: Key features of the included evidence – indirect comparisons

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Ibrutinib vs. chlorambucil						
RESONATE-2	269	R, OL, MC Median 18.4 mths	Unclear	≥65 years; previously untreated CLL/SLL with comorbidities excluding use of fludarabine.	PFS, OS	Survival gain; proportion with AEs
Rituximab+chlorambucil (ritux+chl) vs. chlorambucil; obinutuzumab+chlorambucil (obi+chl) vs. chlorambucil						
CLL11	589	R, OL, MC Median 14.5 mths obi+chl and 15.3 mths ritux+chl	Unclear	Previously untreated CLL with comorbidities.	PFS, OS	Survival gain; proportion with AEs
Ofatumumab+chlorambucil (ofa+chl) vs. chlorambucil						
COMPLEMENT-1	447	R, OL, MC Median 28.9 mths	Low	Previously untreated CLL, considered inappropriate for fludarabine-based therapy.	PFS, OS	Survival gain; proportion with AEs

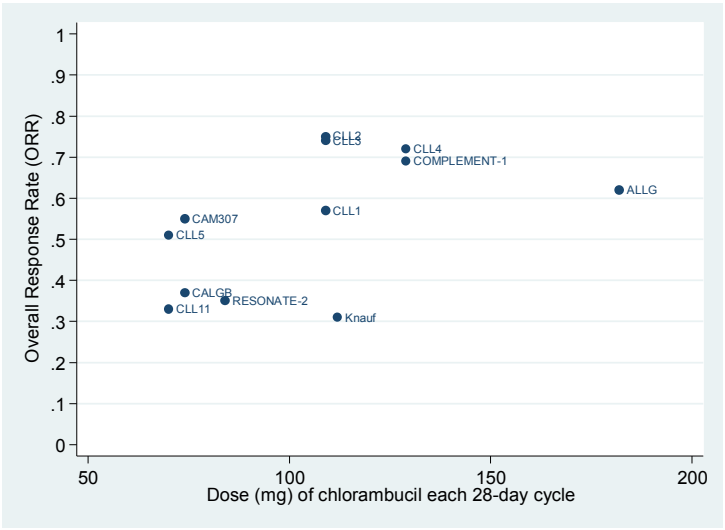
AE=adverse events; MC=multi-centre; mths=months; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised
Source: Table Bii.8, p14 of Section Bii of the submission

6.6 The submission considered that the indirect comparisons were biased against ibrutinib due to the different dosing levels of chlorambucil used across the trials. In RESONATE-2 and COMPLEMENT-1, patients could receive up to 12 cycles of chlorambucil, while in CLL11 a maximum of only 6 cycles was allowed. The submission presented a detailed assessment of chlorambucil dosing in the trials and Australian clinical practice as well as literature assessing the impact of chlorambucil dosing on PFS and response rate. The submission concluded that the comparator arms in RESONATE-2 and CLL11 are not exchangeable and provided a single arm comparison of ibrutinib and obi+chl (see 'Comparative effectiveness' below).

6.7 The median number of cycles of chlorambucil in both CLL11 and COMPLEMENT-1 was 6 (approximately 5.5 months), compared to 7.1 months in RESONATE-2. Although the median cumulative chlorambucil dose in the COMPLEMENT-1 trial was higher than in CLL11, the dose was not much higher than that observed in RESONATE-2 (728mg versus 600mg). The median cumulative dose in CLL11 was 384mg.

6.8 The ESC noted the arguments put forward in the PSCR (p2) however considered the analysis of comparative doses of chlorambucil and the overall response rate (ORR) (as presented in Figure 3 below) was flawed given it did not take account of the number of cycles of treatment. Figure 3 shows the difference between the CLL11 and RESONATE-2 cumulative chlorambucil dosing and response was not vastly different as indicated by the similar ORR in Figure 3 (33% in CLL11 vs 35% in RESONATE-2). The ESC also noted titration of chlorambucil dosing was allowed in these trials. The PBAC reiterated its previous consideration (November 2014 ofatumumab PSD, paragraph 7.4) that variations in the chlorambucil dosing when used as a common comparator was not a significant issue.

Figure 3: Per-cycle dose of chlorambucil and overall response rate



Source: Figure 3, PSCR, p5.

6.9 The bulk of the evidence presented by the submission was based on the May 2015 data cut of RESONATE-2. However, PFS and OS results used in the economic model were based on an updated data cut from February 2016. Limited PFS data were available for this updated analysis (see 'Comparative effectiveness' below), with only hazard ratios provided, while the updated results for OS had more complete data.

The ESC noted the reliance on the May 2015 data cut in the clinical assessments and requested updated data if available, or if not available an indication of when it will be. The PBAC noted no further updated data was provided in the pre-PBAC response.

Comparative effectiveness

6.10 The submission provided results for both investigator-assessed and Independent Review Committee (IRC)-assessed PFS. The IRC-assessed PFS was the primary endpoint in RESONATE-2. The investigator-assessed results were used in the economic evaluation.

6.11 The following table provides a summary of investigator-assessed PFS across the trials, along with the results of the indirect comparisons for the May 2015 data cut of RESONATE-2, followed by available results for the February 2016 data cut. The updated results included updated results for CLL11 (initial data cut May 2013; updated data cut April 2014), re-constructed from figures in the published paper (data for COMPLEMENT-1 was not updated).

Table 4: Summary of results of the indirect comparisons based on investigator-assessed PFS (May 2015 data cut for RESONATE-2)

Trial	Outcome	Ibr n/N (%)	Chl n/N (%)	Absolute difference	HR (95% CI)
RESONATE-2 ibr vs. chl	Progressed	6/136 (4.4%)	64/133 (48.1%)	-	-
	Median months PFS	NR	15 (10.2, 18.9)	-	0.09 (0.04, 0.17)
Comparators		**Intervention n/N (%)**	**Chl n/N (%)**	**Absolute difference**	**HR (95% CI)**
CLL11 ritux+chl vs chl	Progressed	NA	NA	-	
	Median months PFS	16.3	11.1	5.2 mths	0.44 (0.34, 0.57)
Indirect comparison ibr vs. ritux+chl					[redacted]
CLL11 obi+chl vs. chl	Progressed	NA	NA	-	-
	Median months PFS	26.7	11.1	15.6 mths	0.18 (0.13, 0.24)
Indirect comparison ibr vs. obi+chl					[redacted]
COMPLEMENT-1 ofa+chl vs. chl	Progressed	NA	NA	-	-
	Median months PFS	23.4	14.5	8.9 mths	0.54 (0.41, 0.69)
Indirect comparison ibr vs. ofa+chl					[redacted]

Source: Table Bi.28, p88 of Section Bi of the submission; Table Bii.29, p58; Table Bii.30, p58 of Section Bii of the submission.
chl=chlorambucil; HR=hazard ratio; ibr=ibrutinib; NA=not available; NR=not reported; obi+chl=obinutuzumab+chlorambucil; ofa+chl=ofatumumab+chlorambucil; ritux+chl=rituximab+chlorambucil; **bold**=statistically significant.

Table 5: Summary of results of the indirect comparisons based updated investigator-assessed PFS for RESONATE-2 (February 2016) and CLL11 (April 2014)

Trial	Outcome	Ibr n/N (%)	Chl n/N (%)	Absolute difference	HR (95% CI)
RESONATE-2 ibr vs. chl	Progressed	NA	NA	-	-
	Median months PFS	NA	NA	-	[redacted]
Comparators		**Intervention n/N (%)**	**Chl n/N (%)**	**Absolute difference**	**HR (95% CI)**
CLL11 ritux+chl vs chl	Progressed	NA	NA	-	
	Median months PFS	NA	NA	-	**0.45 (0.35, 0.57)**
Indirect comparison ibr vs. ritux+chl					[redacted]
CLL11 obi+chl vs. chl	Progressed	NA	NA	-	-
	Median months PFS	NA	NA	-	**0.19 (0.15, 0.25)**
Indirect comparison ibr vs. obi+chl					[redacted]
COMPLEMENT-1 ofa+chl vs. chl	Progressed	NA	NA	-	-
	Median months PFS	23.4	14.5	8.9 mths	0.54 (0.41, 0.69)
Indirect comparison ibr vs. ofa+chl					[redacted]

Source: Table Bi.28, p88 of Section Bi of the submission; Table Bii.29, p58; Table Bii.30, p58 of Section Bii of the submission.
chl=chlorambucil; HR=hazard ratio; ibr=ibrutinib; NA=not available; NR=not reported; obi+chl=obinutuzumab+chlorambucil; ofa+chl=ofatumumab+chlorambucil; PFS=progression-free survival; ritux+chl=rituximab+ chlorambucil; bold=statistically significant.

6.12 The ESC noted there is a trend to less favourable indirect comparison results in the updated data, which is consistent across all comparators (see Tables 4 and 5 above).

6.13 Based on the May 2015 data cut of RESONATE-2, only [redacted] patients in the ibrutinib arm had a progression event, and median PFS was not reached. The indirect comparisons demonstrated statistically significant advantages for ibrutinib compared to ritux+chl and ofa+chl, but there was no statistically significant advantage for ibrutinib compared to obi+chl, for both the original and updated analyses.

6.14 The PBAC has previously concluded that obi+chl provided a significant improvement in efficacy over ritux+chl (March 2015 obinutuzumab PSD, paragraph 7.2). Consistent with this, a recent systematic review and meta-analysis (Stadler 2016) of interventions for unfit patients with CLL demonstrated a significant advantage for obi+chl compared to both ritux+chl and ofa+chl.

6.15 The submission's proposed blended comparator pools treatments with different efficacy; further, superiority over the most effective regimen (obi+chl) has not been demonstrated.

6.16 Results for Independent review Committee (IRC)-assessed PFS are provided in the following table (May 2015 data cut for RESONATE-2).

Table 6: Summary of results of the indirect comparisons based on IRC-assessed PFS

Trial	Outcome	Ibr n/N (%)	Chl n/N (%)	Absolute difference	HR (95% CI)
RESONATE-2 ibr vs. chl	Progressed	12/136 (8.8%)	57/133 (42.9%)	-	-
	Median months PFS	NR	18.9 (14.1, 22.0)	-	**0.16 (0.09, 0.28)**
Comparators		**Intervention n/N (%)**	**Chl n/N (%)**	**Absolute difference**	**HR (95% CI)**
CLL11 ritux+chl vs chl	Progressed	NA	NA	-	
	Median months PFS	16.1	11.2	4.9 mths	**0.46 (0.35, 0.61)**
Indirect comparison ibr vs. ritux+chl					[redacted]
CLL11 obi+chl vs. chl	Progressed	NA	NA	-	-
	Median months PFS	27.2	11.2	16.0 mths	**0.19 (0.14, 0.27)**
Indirect comparison ibr vs. obi+chl					[redacted]
COMPLEMENT-1 ofa+chl vs. chl	Progressed	NA	NA	-	-
	Median months PFS	22.4	13.1	9.3 mths	0.57 (0.45, 0.72)
Indirect comparison ibr vs. ofa+chl					[redacted]

Source: Table Bi.28, p88 of Section Bi of the submission; Table Bii.29, p58; Table Bii.30, p58 of Section Bii of the submission.
chl=chlorambucil; HR=hazard ratio; ibr=ibrutinib; IRC=Independent Review Committee; NA=not available; NR=not reported; obi+chl=obinutuzumab+chlorambucil; ofa+chl=ofatumumab+chlorambucil; PFS=progression-free survival; ritux+chl=rituximab+ chlorambucil; bold=statistically significant.

6.17 The results of IRC-assessed PFS followed the same pattern as those for investigator assessed, with statistically significant advantage for ibrutinib compared to ritux+chl and ofa+chl, but no statistically significant difference between ibrutinib and obi+chl. The hazard ratios for the indirect comparisons based on investigator assessed PFS rather than IRC-assessed PFS are more favourable for ibrutinib, and the use of investigator assessed PFS in the economic model is likely to have resulted in lower ICERs than if IRC-assessed PFS was used.

6.18 The submission provided an additional single arm comparison of ibrutinib and obi+chl using investigator-assessed PFS, because of the differences in chlorambucil dosing across the trials used in the indirect comparison. This comparison showed a significant advantage for ibrutinib ([redacted]; 95% CI: [redacted]). The ESC agreed with the PBAC's previous consideration that variations in chlorambucil dosing when used as a common comparator is not a significant issue (November 2014 ofatumumab PSD, paragraph 7.4); therefore this is not sufficient justification for relying on a single arm comparison in preference to an indirect comparison based on randomised trials.

6.19 A publication identified during the evaluation (authored by employees of the sponsor) reported the results of a matching-adjusted indirect comparison (MAIC) of ibrutinib and obi+chl (van Sanden 2017). In this comparison patients were excluded from RESONATE-2 who did not match the CLL11 inclusion criteria (based on Cumulative Illness Rating Scale (CIRS) score and creatinine clearance) and for the remaining patients, weights were assigned so that the re-weighted population more closely resembled the CLL11 population (the process is similar to propensity score weighting). Then the updated hazard ratio from RESONATE-2 was compared to the hazard ratio from CLL11 using a Bayesian indirect comparison.

6.20 The MAIC-based comparison indicated an advantage for ibrutinib compared to obi+chl (HR=0.12 95% CI: 0.02, 0.97). The matching done in this analysis was based on CIRS score, age, Binet stage, creatinine clearance and other variables that were

not highlighted as differences between the trials by the submission. Also, the effective sample size following matching was 35. While the treatment effect became larger using MAIC, the sample size upon which it was based is considerably smaller. van Sanden (2017) acknowledges that MAIC is a relatively new technique, and the small effective sample size suggests caution should be used when interpreting the results.

6.21 The ESC noted the Xu et al (2017) Bayesian network meta-analysis (NMA) and van Sanden (2017) MAIC analysis referenced in the PSCR (p3). Of these two additional analyses, the ESC considered the MAIC was the more robust analysis given its superior control of confounder imbalance between included trials. However, the penalty with this approach is the characteristically wider credible intervals that result from matching. The post-matching intervals for the ibrutinib vs obi+chl comparison were very wide (PFS: 0.02, 0.97; OS: 0.00 to 8.89). Thus, whilst the crude probability comparisons appear to support a treatment advantage favouring ibrutinib, consideration of the credible intervals do not support such a benefit.

6.22 With respect to the Xu (2017) NMA, the ESC noted that, as with the MAIC, whilst the point estimate Hazard Ratios from the NMA suggest both a PFS and OS benefit favouring ibrutinib relative to comparator therapies, the specific comparison to obi+chl remains non-significant and associated with relatively high upper limits of the credible interval (1.61 for PFS; 1.51 for OS).

6.23 Results for the indirect comparisons of overall survival are provided in the table below. Median OS was not reached in any of the trials. In the RESONATE-2 trial only 3 (2.2%) patients in the ibrutinib arm had died.

Table 7: Summary of results of the indirect comparisons - overall survival

Trial	Outcome	Ibr n/N (%)	Chl n/N (%)	Absolute difference	HR (95% CI)
RESONATE-2 ibr vs. chl	Dead	3/136 (2.2%)	17/133 (12.8%)	-	-
	Median months OS	NR	NR	-	**0.16 (0.05, 0.56)**
Comparators		**Intervention n/N (%)**	**Chl n/N (%)**	**Absolute difference**	**HR (95% CI)**
CLL11 ritux+chl vs chl	Dead	NA	NA	-	-
	Median months OS	NR	NR	-	0.66 (0.41, 1.06)
Indirect comparison ibr vs. ritux+chl					[redacted]
CLL11 obi+chl vs. chl	Dead	NA	NA	-	
	Median months OS	NR	NR	-	**0.41 (0.23, 0.74)**
Indirect comparison ibr vs. obi+chl					[redacted]
COMPLEMENT-1 ofa+chl vs. chl	Dead	NA	NA	-	-
	Median months OS	NR	NR	-	0.91 (0.57, 1.43)
Indirect comparison ibr vs. ofa+chl					[redacted]

Source: Table Bi.28, p88 of Section Bi of the submission; Table Bii.29, p58; Table Bii.30, p58 of Section Bii of the submission.
chl=chlorambucil; HR=hazard ratio; ibr+chl=ibrutinib+ chlorambucil; IRC=Independent Review Committee; NR=not reached; obi+chl=obinutuzumab+chlorambucil; ofa+chl=ofatumumab+chlorambucil; OS=overall survival; ritux+chl=rituximab+chlorambucil; **bold**=statistically significant.

6.24 The results of the indirect comparisons for OS followed a similar pattern to the results for PFS, with statistically significant advantages for ibrutinib compared to ritux+chl and compared to ofa+chl, but no statistically significant advantage for ibrutinib compared to obi+chl.

6.25 The submission provided updated OS results for RESONATE-2, based on the February 2016 data cut [redacted] deaths for ibrutinib compared to [redacted] deaths in the

chlorambucil arm (HR=0.44; 95% CI: 0.21, 0.92)). At this data cut 41% of patients randomised to chlorambucil had crossed over to ibrutinib (after progression). The PBAC noted that the updated OS results from February 2016 are less favourable than the May 2015 data cut (HR of 0.44 vs 0.16) (see Figure 4). The submission also reported updated OS results for CLL11 although only hazard ratios for the comparisons between ritux+chl and obi+chl were available. The submission did not provide statistical comparisons of these updated OS results.

Figure 4: Overall Survival (ITT population) February 2016 data cut

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

Comparative harms

6.26 The table below provides a summary of adverse events in the trials, as well as results of the indirect comparisons presented by the submission. The submission did not provide any statistical comparisons of individual adverse events (eg neutropenia), but it did provide a listing of the most frequent (>5%) AEs ≥Grade 3. With the exception of infusion-related reactions associated with the intravenous administration of obinutuzumab, rituximab and ofatumumab, the most frequent AEs ≥ Grade 3 were largely similar across the drugs:

- Ibrutinib (RESONATE-2): neutropenia, anaemia, infections and infestations
- Obi+chl (CLL11): neutropenia, infusion-related reactions, thrombocytopenia, infections, anaemia, leukopenia
- Ritux+chl (CLL11): neutropenia, infections, pneumonia
- Ofa+chl (COMPLEMENT-1): neutropenia, infusion-related reactions, infections, thrombocytopenia, anaemia

Table 8: Summary of adverse event comparisons

Trial	Treatment	n/N (%)		Direct comparisons		Indirect comparisons	
		Intervention	Chl	RR (95% CI)	RD (95% CI)	RR (95% CI)	RD (95% CI)
Severe AE (≥ Grade 3)							
RESONATE-2	Ibr	[redacted]	[redacted]	[redacted]	[redacted]	-	-
CLL11	Ritux+chl	125/225 (55.6%)	58/116 (50.0%)	**1.11 (0.90,1.38)**	**5.6 (- 5.6, 16.7)**	[redacted]	[redacted]
	Obi+chl	175/241 (72.6%)	58/116 (50.0%)	**1.45 (1.19, 1.77)**	**22.6 (11.9, 33.3)**	[redacted]	[redacted]
COMPLEMENT-1	Ofa+chl	109/217 (50.2%)	98/227 (43.2%)	**1.16 (0.95, 1.42)**	**7.1 (-2.2, 16.3)**	[redacted]	[redacted]
Treatment-related AE							
RESONATE-2	Ibr	[redacted]	[redacted]	[redacted]	[redacted]	-	-
CLL11	Ritux+chl	NR	NR	NR	NR	NC	NC
	Obi+chl	NR	NR	NR	NR	NC	NC
COMPLEMENT-1	Ofa+chl	182/217 (83.9%)	148/227 (65.2%)	**1.29 (1.15, 1.44)**	**18.7 (10.8, 26.6)**	[redacted]	[redacted]
Withdrawal due to AE							
RESONATE-2	Ibr	[redacted]	[redacted]	[redacted]	[redacted]	-	-
CLL11	Ritux+chl	16/225 (7.1%)	16/116 (13.8%)	**0.52 (0.27, 0.99)**	-6.7 (-13.8, 0.4)	[redacted]	[redacted]
	Obi+chl	33/241 (13.7%)	16/116 (13.8%)	0.99 (0.57, 1.73)	-0.1 (-7.7, 7.5)	[redacted]	[redacted]
COMPLEMENT-1	Ofa+chl	28/217 (12.9%)	29/227 (12.8%)	1.01 (0.62, 1.64)	0.1 (-6.1, 6.4)	[redacted]	[redacted]

Chl=chlorambucil; Ibr=ibrutinib; NC=not calculable; NR=not reported; Obi=obinutuzumab; Ofa=ofatumumab; RD=risk difference; RR=relative risk; **bold**=statistically significant

Source: Table Bii.49, p91 and Table Bii.50, p92 of Section Bii of the submission.

6.27 The indirect comparisons indicated no statistically significant differences between ibrutinib and the comparators for severe AEs or treatment-related AEs, although there were significantly more withdrawals due to AEs for obi+chl and ofa+chl compared to ibrutinib. The difference in the withdrawal rates for the common arm ([redacted]% for RESONATE-2 vs 12.8% for COMPLEMENT-1 and 13.8% for CLL11) limit the conclusions that can be drawn from this comparison. For the comparison of ibrutinib and obi+chl, the statistically significant difference was observed based on risk difference only, while the relative risk analysis did not return a significant result.

6.28 The submission concluded that ibrutinib has a numerically similar overall incidence of adverse events but a different AE profile than the comparators, which would be expected when comparing a non-cytotoxic treatment with a cytotoxic chemotherapy treatment.

6.29 The PBAC identified the occurrence of atrial fibrillation (AF) with ibrutinib in relation to the November 2016 ibrutinib submission for relapsed/refractory mantle cell lymphoma. The PBAC noted emerging data suggesting ibrutinib may be associated with an increased risk of AF (paragraph 7.7, November 2016 ibrutinib PSD). The PBAC also considered that the costs associated with monitoring for AF should be included in the economic model and financial forecasts for any re-submission for mantle cell lymphoma (paragraph 7.8, November 2016 ibrutinib PSD).

6.30 The submission reported AF data from RESONATE-2. The submission reported that AF was reported in 8 patients (5.9%) and atrial flutter in [redacted]; and [redacted] discontinued due to AF. AF was reported for 1 patient (0.8%) in the chlorambucil arm of the trial. The submission claimed that in general AF was a transient event resulting in infrequent discontinuation of ibrutinib, and that based on post-marketing data, the reporting rate of AF was comparable to the expected background rates of AF in the general population (p126 of Section Bi of the submission).

6.31 During the evaluation the following articles discussing AF with ibrutinib were identified:

- Asnani 2016: The paper stated that specific targeted therapies such as ibrutinib may contribute directly to the development of AF. The Asnani paper went on to describe occurrence of AF in clinical trials of ibrutinib (eg RESONATE, mantle cell lymphoma) and stated that elucidation of the molecular mechanisms underlying the development of AF will become increasingly important as indications for ibrutinib and other BTK inhibitors expand over time.

- Thompson 2016: This paper described a retrospective study of patients being treated for CLL who developed AF on ibrutinib (n=56). This study found that AF onset generally occurred between 3 and 8 months after initiation of ibrutinib and 76% of patients developed AF during the first year of therapy.

- Vrontikis 2016: On the basis that ibrutinib-related AF occurs in up to 11% of patients in clinical trials, the Vrontikis paper presented a proposed algorithm for managing ibrutinib-related AF.

- Leong 2016: The authors conducted a systematic review and meta-analysis to estimate the magnitude of the increase in AF risk among ibrutinib recipients as compared to alternative therapies and to quantify the frequency of AF reported among ibrutinib recipients. A total of 20 trials were included in the overall meta-analysis. The pooled rate of AF among ibrutinib recipients across all 20 trials was 3.3 (95% CI: 2.5, 4.1) per 100 person-years while the pooled rate of AF among participants receiving non-ibrutinib therapy in the trials was 0.84 (95% CI: 0.32, 1.6) per 100 person-years. Based on analysis of 4 randomised trials of ibrutinib, the pooled relative risk of AF associated with ibrutinib versus the comparator was 3.5 (95% CI: 1.8, 6.9).

6.32 The ESC noted there is also an increased risk of bleeding in patients taking ibrutinib and it is contraindicated in patients with high bleeding risk including those who are on anticoagulant medications. Haemorrhage and bruising are listed as very common treatment-emergent adverse drug reactions in the ibrutinib Product Information, with other common events being subdural haematoma, petechiae, and epistaxis. The incidence is decreased in subsequent clinical trials including RESONATE-2 likely due to stringent exclusion criteria of patients at high bleeding risk.

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

Benefits and harms

6.33 The indirect comparisons demonstrated a statistically significant reduction in the risk of progression and death with ibrutinib compared with ritux+chl and ofa+chl. The magnitude of the benefits cannot be reliably quantified because of the low number of events in the trials, and in particular in the ibrutinib trial.

6.34 The indirect comparisons did not demonstrate a statistically significant reduction in the risk of progression and death with ibrutinib compared with obi+chl.

6.35 On the basis of the indirect comparisons there were no statistically significant differences in severe adverse events (≥Grade 3) or treatment-related adverse events. An increased risk of atrial fibrillation has been observed with ibrutinib treatment for CLL as well as other indications.

Interpretation of clinical evidence

6.36 The submission claimed that ibrutinib has superior comparative effectiveness when compared to obi+chl, ritux+chl and ofa+chl. In regard to safety, the submission claimed that ibrutinib was non-inferior to the comparators, with a numerically similar incidence of adverse events but with a different safety profile, as would be expected when comparing a non-cytotoxic treatment with a cytotoxic chemotherapy regimen.

6.37 In regard to the claim of superior comparative effectiveness, while the evidence presented by the submission indicated statistically significant advantages for ibrutinib compared to ritux+chl and ofa+chl, there was no statistically significant advantage for ibrutinib in terms of PFS or OS compared to obi+chl.

6.38 The submission considered that due to differences in chlorambucil dosing in RESONATE-2 and CLL11, the indirect comparisons were biased against ibrutinib. On the basis of a single arm comparison using data from RESONATE-2 and CLL11, the submission claimed a statistically significant advantage in PFS for ibrutinib compared to obi+chl. The PBAC reiterated that the variations in chlorambucil dosing were not a significant issue and it was not appropriate to replace an indirect comparison with a single arm comparison on the basis of differences in chlorambucil dosing.

6.39 In regard to the claim of superior comparative effectiveness, the ESC considered while the evidence presented by the submission indicated statistically significant advantages for ibrutinib compared to ritux+chl and ofa+chl, there was no statistically significant advantage for ibrutinib in terms of PFS or OS compared to obi+chl. The PBAC agreed with the ESC conclusion.

6.40 While the claim of non-inferior safety between ibrutinib and the comparators was supported by the indirect comparisons presented in the submission, emerging data suggest that there is an increased risk of AF associated with ibrutinib. The PBAC agreed with this claim.

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

Economic analysis

6.41 The submission presented a cost-utility analysis (CUA) against a blended comparator of obi+chl, ritux+chl and ofa+chl. The comparator weighting was based on PBS usage data from May 2016 to April 2017 (rituximab 61.3%; obinutuzumab 29.4%; ofatumumab 9.3%). Given that the indirect comparisons presented by the submission demonstrated no statistically significant advantage for ibrutinib compared to obi+chl, the use of a weighted comparator was not supported. The ESC considered on the basis of the available evidence, rather than assuming ibrutinib is better than all PBS-subsidised first-line therapies, a more appropriate approach to the economics may be CUA vs ritux+chl with a comparable ICER to obi+chl vs ritux+chl from March 2015 ($15,000/QALY - $45,000/QALY) or a cost-minimisation analysis (CMA) vs obi+chl. The ESC noted that accounting for differences in dosing regimens and immature PFS data complicates CMA with respect to estimating treatment duration.

6.42 The submission's model used 3 health states (unprogressed, progressed, dead) and 3 lines of treatment — so once progressed a patient would move to unprogressed in the next line of treatment. For the comparator arm ibrutinib is included as one of the subsequent treatments for progressed patients (specifically as second-line treatment) and hence the reduced use of ibrutinib as a later-line treatment contributes to the establishment of cost-effectiveness of ibrutinib as first-line treatment. The ibrutinib price used for progressed patients (ie in the relapsed/refractory (R/R) setting) in the economic model is the same as proposed for first line. As noted in Section 2 above this is higher than the price considered cost-effective by the PBAC and this results in the ICER being underestimated. The PSCR (p1) updated the price of ibrutinib in second-line, which increased the ICER by approximately $[redacted]/QALY. The PSCR still underestimated the ibrutinib price and ICER as not all aspects of the RSA were included.

6.43 In its original evaluation of obinutuzumab for treatment of CLL the PBAC had requested an additional health state to account for patients who are progressed but well, and 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 (paragraph 7.13, July 2014 obinutuzumab PSD). The ibrutinib model includes the lower utility ([redacted]) for asymptomatic progression in the first-line of treatment, with an extra decrement of [redacted] for the last cycle of progression before death or second-line treatment to account for symptomatic progression.

6.44 The table below provides a summary of the model structure.

Table 9: Summary of model structure and rationale

Component	Summary
Time horizon	20 years in the model base case versus 14.5-28.9 months of median follow up in the trials.
Outcomes	LYG; QALYs
Methods used to generate results	Markov cohort model based on piecewise exponential regression from RESONATE-2 data with hazard ratio data calculated from indirect comparisons of ibrutinib and obinutuzumab, rituximab and ofatumumab.
Comparison	Ibrutinib → Ritux+Chl → 3rd line treatment Versus Ritux+Chl →Ibrutinib → 3rd line treatment (61.3%) Obi+Chl → Ibrutinib → 3rd line treatment (29.4%) Ofa+Chl → Ibrutinib → 3rd line treatment (9.3%)
Health states	Unprogressed, progressed, death; plus patients can start a new treatment (second or third-line therapy) where they move to unprogressed for the new treatment.
Utilities	Trial-based EQ-5D values from RESONATE-2 for first-line treatment; literature based for second and third-line treatment.
Cycle length	30 days with no half cycle correction
Transition probabilities	PFS transition probabilities were based on RESONATE-2 data as well as CLL11 and COMPLEMENT-1 for the comparators. Time to progression for further lines of therapy were adjusted by multipliers based on the CLL8 and REACH trials used in first and second-line treatment of CLL with rituximab-fludarabine-cyclophosphamide.

LYG=life years gained; QALYs=quality-adjusted life years

Source: Section D.3.3.2, p10-11; Section D.3.3.3, p11-12 and Table D.2, p14 of Section D of the submission; Section C.2.12, p42-49 of Section C of the submission.

6.45 The following table provides a summary of the key drivers of the model.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Time horizon	20 years based on a median of 18 months follow-up in RESONATE-2. The low number of clinical events observed in the trials results in substantial uncertainty when the results are extrapolated over a long time period. With an analysis restricted to a time horizon based on the trials, the incremental LYs gained is [redacted] years. Extending the time horizon to 20 years increases the incremental LYs gained to [redacted] years. Thus [redacted]% of the incremental gain in LYs is based on extrapolated rather than trial data. The patient population enter the model at 73 years of age and will likely have comorbidities, which further suggests a time horizon of less than 20 years may be more appropriate. The PBAC previously considered a 10 year time horizon to be appropriate for obinutuzumab in first-line and also for ibrutinib in relapsed/refractory patients. The ESC agreed that 20 years was optimistic given the average age of patients commencing first line treatment is >70 years.	High, favours ibrutinib
Utilities	While utility values are trial-based for first-line treatment the model was sensitive to alternate literature-based values.	High
Comparator	The model used a blended or weighted comparator.	High, favours ibrutinib
Efficacy of ibrutinib versus comparators	The efficacy estimates for ibrutinib versus the comparator treatments were based on indirect comparisons. The efficacy analyses indicated no statistically significant advantage for ibrutinib over obi+chl, however an efficacy difference is incorporated into the model.	High, favours ibrutinib

Source: Table D.2, p14 of Section D of the submission

6.46 The figure below presents the difference in progression modelled for the first treatment. The modelled reduction in time to progression with ibrutinib compared with the comparator treatments is large, and the difference between ibrutinib and obi+chl is not supported by the non-significant outcomes for the indirect comparison

and is substantially larger than the difference between obi+chl and rit+chl which appears inconsistent with the efficacy results previously considered by the PBAC.

Figure 5: Modelled proportion of patients who have yet to progress at first-line, by first-line treatment

Source: Major submission, Section D, Figure D.4 page 32

6.47 The table below provides the results of the stepped economic evaluation. As the model uses 3 lines of treatment, and the base case ICER is based on a blended, or weighted combination of these comparators, results using the agent considered superior by the PBAC (obinutuzumab) are also included. All costs and ICERs are slightly different than those presented in the submission as ibrutinib and rituximab prices were updated to 1 July 2017 dispensing and AHI fees.

Table 11: Results of the stepped economic evaluation[a]

Step and component	Ibrutinib	Blended comparator[b] Ritux+chl; obi+chl; ofa+chl	Increment
Step 1: trial-based costs and outcomes *(treatment algorithm included for outcomes but not costs)*			
Costs	[redacted]	[redacted]	[redacted]
LYG	[redacted]	[redacted]	[redacted]
Incremental cost/extra LYG gained			[redacted]
Step 2: time horizon extended to 20 years			
Costs	[redacted]	[redacted]	[redacted]
LYG	[redacted]	[redacted]	[redacted]
Incremental cost/extra LYG gained			[redacted]
Step 3: discounting (5%) included			
Costs	[redacted]	[redacted]	[redacted]
LYG	[redacted]	[redacted]	[redacted]
Incremental cost/extra LYG gained			[redacted]
Step 4: all costs (adverse events, drug administration) included *(treatment algorithm added for costs)*			
Costs	[redacted]	[redacted]	[redacted]
LYG	[redacted]	[redacted]	[redacted]
Incremental cost/extra LYG gained			[redacted]
Step 5: utility weights applied			
Costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost/extra QALY gained (base case)			[redacted]
Compared to obinutuzumab+chlorambucil first line			
	Ibrutinib	**Obi+chl first-line**	**Increment**
Costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost/extra QALY gained			[redacted]

[a] During the evaluation, for ibrutinib the dispensing fee and Administration, Handling and Infrastructure (AHI) fee were updated to 1 July 2017 values. For rituximab, the wholesale, diluent, preparation and dispensing fees were updated to 1 July 2017 values.

[b] Costs for comparator treatments in the first 3 steps are for first-line treatment only ie up to 6 cycles of obi+chl, 6 cycles of ritux+chl, and 12 cycles of ofa+chl, weighted as per section paragraph 6.40 above.

Source: Table D.5, p30 and Excel workbook 'Section D.xlsm' of the submission.

6.48 The base case ICER is $75,000/QALY - $105,000/QALY. The ICER increases to $75,000/QALY - $105,000/QALY if first-line comparator treatment is obi+chl instead of the blended comparator, although it should be noted that this is based on the assumption of superior PFS and OS with ibrutinib.

6.49 The modelled time horizon was 20 years based on a median of 18 months follow-up in RESONATE-2. The submission justified the model time horizon of 20 years on the basis that the PBAC Guidelines (v4.4) recommend a full life expectancy time horizon for the management of cancer. The low number of clinical events observed in the trials results in substantial uncertainty when the results are extrapolated over a long time period. With an analysis restricted to a time horizon based on the trials, the incremental LYs gained were [redacted] years (Step 1, Table 12). Extending the time horizon to 20 years increased the incremental LYs gained to [redacted] years (Step 2, Table 12). Thus [redacted]% of the incremental gain in LYs was based on extrapolated rather than trial data. The PBAC previously considered a 10 year time horizon to be appropriate for obinutuzumab in first-line CLL and for ibrutinib in relapsed/refractory CLL. Application of a 10 year time horizon to the current model resulted in an ICER of $75,000/QALY - $105,000/QALY. The PSCR (p4) argued 20 years is more appropriate, based on the fact the 10 year time horizon was used in the ibrutinib relapsed/refractory submission, and first line would expect longer survival, and the model estimates that [redacted]% of ibrutinib patients remain progression free at the end

of 10 years. The ESC noted that the modelled [redacted]% of patients remaining progression free at 10 years was based on favourable assumptions of ibrutinib efficacy; further, the ESC noted that the 20 years was optimistic given the average age of patients commencing first line treatment is >70 years.

6.50 As well as time horizon and nominated first-line treatment, the model is also sensitive to utility values. If literature-based utility values are used for first-line treatment instead of trial-based values the ICER increased, becoming $75,000 – $105,000using values from Ferguson (2009) and $75,000 – $105,000 when values from Kosmas (2015) were applied.

Table 12: Results of sensitivity analyses[a]

Analyses	Incremental cost	Incremental QALY	ICER
Base case	[redacted]	[redacted]	[redacted]
Time horizon (base case: 20 years) 15 years 10 years	[redacted]	[redacted]	[redacted]
Mean age (base case 73 years)			
60 years 85 years	[redacted]	[redacted]	[redacted]
Utility values (base case RESONATE-2)			
Kosmas Ferguson	[redacted]	[redacted]	[redacted]
Alternate first line therapy (base case: blended comparator)			
Obi+chl first line therapy Ritux+chl first line therapy Ofa+chl first line therapy	[redacted]	[redacted]	[redacted]
Multivariate analyses			
10 year time horizon and obi+chl first-line 10 year time horizon and Kosmas utility values Kosmas utility values and obi+chl first line	[redacted]	[redacted]	[redacted]

[a] During the evaluation, for ibrutinib the dispensing fee and Administration, Handling and Infrastructure (AHI) fee were updated to 1 July 2017 values. For rituximab, the wholesale, diluent, preparation and dispensing fees were updated to 1 July 2017 values.

6.51 Source: Table D.7, p39 of Section D of the submission and Excel workbook 'Section D.xlsm'. Based on the sensitivity analyses presented in the submission the ICER ranged from $75,000/QALY - $200,000/QALY per QALY gained. This range does not reflect the uncertainty with the model inputs, and specifically the uncertainty associated with the efficacy estimates based on small number of clinical events and indirect comparisons.

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

Drug cost/patient/year: $[redacted]

6.52 Ibrutinib is a monthly treatment that continues until disease progression. The proposed effective cost per year is $[redacted] per month*[redacted] scripts per year*[redacted]% dose intensity = $[redacted]. In the economic model ibrutinib therapy was assumed to continue for approximately 7.5 years at a modelled cost of $[redacted].

6.53 The comparators have limited courses of therapy over 6-12 months (see table below).

Table 13: Estimated drug cost/patient/course of comparators (published prices)

Drug	Drug cost per cycle*		No of cycles per course		Chl cost per cycle	Cost per course
Ritux+chl	$2,591.32	$3,302.48	1	5	$83.35	$19,604
Obi+chl	$15,484.08	$5,161.36	1	5	$83.35	$41,791
Ofa+chl	$4,411.96	$3,337.03	1	11	$83.35	$42,119

*dispensed price weighted for use in public vs private and includes adjustment for assumed dose intensity of 94.5%.
^ 10mg/m^2/day dose for 7 days of each 28 day cycle as per eviQ protocol and includes adjustment for assumed dose intensity of 95.6%.
chl=chlorambucil; ibr=ibrutinib; obi=obinutuzumab; ofa=ofatumumab; ritux=rituximab
Source: Excel workbook 'Section D.xlsm' and Section E Table E.1.

Estimated PBS usage & financial implications

6.54 This submission was considered by DUSC. The submission applied an epidemiological approach to estimate expected use and cost of ibrutinib for first-line treatment of CLL/SLL over the first 5 years of listing. Key components of the financial estimates are as follows:

- The epidemiological approach used by the submission to estimate patient numbers is based on incident patients.
- Market research is used to determine the proportion of patients who are treated and uptake of treatment ([redacted]%) was based on the DUSC assumption applied for the relapsed/refractory CLL/SLL PBS listing.
- Treatment sequences and treatment duration were based on estimates from the economic model.
- The weighting of substituted medicines was based on PBS usage data (ritux+chl 61.3%; obi+chl 29.4%; ofa+chl 9.3%).

The table below provides a summary of estimated patient numbers, scripts and costs to PBS and the Government. Estimated net costs over the first 5 years of listing are more than $100 million.

Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number of *incident* patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib treatment months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib packs[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of ibrutinib					
Cost to PBS/RPBS[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient co-payment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications for substituted therapies					
Cost to PBS/RPBS[b]:					
Rituximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obinutuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib second-line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chlorambucil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pegfilgastrim/G-CSF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Co-payments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost substituted drugs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net financial implications					
Net cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of MBS infusions[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall net cost to Government	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note:

[a] [redacted]

[b] Drug prices were updated during the evaluation to include dispensing fees and preparation fees as of 1 July 2017.

[c] The submission assumes that the substitution of rituximab, obinutuzumab and ofatumumab, administered as intravenous infusions, with oral ibrutinib will result in less claims for the MBS infusion item 13918.

Source: Table E.7, p16 and Table E.13, p22 of Section E of the submission.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be $30 - $60 million per year.

6.55 DUSC considered the estimates presented in the submission to be underestimated. The main issues were:

- Failure to include prevalent patients in the eligible patient population underestimated patient numbers. This included the lack of an estimate of the prevalent pool of untreated patients with diagnosed CLL or SLL.
- Use of treatment sequences and treatment durations were based on the economic model that is not likely to reflect usage and cost in practice.
- Potential for use beyond expectations given a lack of criteria to define unfit patients.

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

Quality use of medicines

6.56 A quality use of medicines program for ibrutinib was outlined in the submission. In particular, the provision of a patient support program to encourage compliance to the prescribed dose and frequency of ibrutinib.

6.57 DUSC noted the potential for the ibrutinib-related AF, and that periodic monitoring of all patients for AF is recommended in the Product Information. DUSC considered that the sponsor should have addressed the management of AF in its submission.

Financial management – risk sharing arrangements

6.58 The submission requested a special pricing arrangement and stated that details of the arrangement would be captured in a Deed of Agreement. The submission did not provide information on details that would be captured in a Deed of Agreement.

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

7 PBAC Outcome

7.1 The PBAC did not recommend the Authority Required listing for ibrutinib for patients with previously untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic leukaemia (SLL) who are unsuitable for treatment with fludarabine-based chemoimmunotherapy. Although the PBAC accepted there is a clinical benefit in progression-free survival (PFS) and overall survival (OS) for ibrutinib when compared to chlorambucil in combination with either rituximab or ofatumumab, the benefit over chlorambucil in combination with obinutuzumab was not proven. The incremental cost-effectiveness ratio presented using the blended comparator of chlorambucil in combination with rituximab, ofatumumab or obinutuzumab was considered high and optimistic.

7.2 The PBAC noted the consumer comments favouring earlier treatment with ibrutinib. However the Committee considered there was no urgent clinical need for most patients, noting the current availability of other effective first-line therapies (all with median PFS of least 16 months and non-inferior toxicity) and the forthcoming PBS listing of ibrutinib in relapsed/refractory patients effective from 1 December 2017.

7.3 The PBAC advised the proposed PBS restriction for first-line treatment would require a prescriber instruction to define patients inappropriate for fludarabine-based therapy, as described above in Section 2.

7.4 The PBAC did not accept the nominated blended (or weighted) comparator of ritux+chl, obi+chl and ofa+chl. The Committee noted the choice of a blended comparator does not reflect previous PBAC findings on the relative efficacy of these treatments. The PBAC previously concluded that obi+chl provided a significant improvement in efficacy over ritux+chl (March 2015 obinutuzumab PSD, paragraph 7.2), and that ritux+chl and ofa+chl were non-inferior (November 2014 ofatumumab PSD, paragraph 7.5). The Committee noted the uptake of obi+chl was increasing (see Figures 1 and 2 above in Section 5), and the ESC advised obi+chl were the preferred treatment option in academic centres as the most effective subsidised therapy. The PBAC agreed with ESC that without robust evidence to justify superiority of ibrutinib vs obi+chl, either non-inferiority to obi+chl and/or superiority of ibrutinib vs ritux+chl would be the most relevant comparisons for assessing clinical and cost-effectiveness of ibrutinib in first-line CLL/SLL.

7.5 The PBAC noted the superior comparative effectiveness of ibrutinib compared to chlorambucil in the key trial RESONATE-2 (at May 2015 cut-off, IRC-assessed PFS HR = 0.16 (0.09, 0.28); investigator-assessed PFS HR = [redacted]; and OS HR = 0.16 (0.05, 0.56)). However, the PBAC noted the small number of events at this cut-off, and that at the February 2016 data cut the relative OS gain had reduced (from HR 0.16 to 0.44). The PBAC noted there was no statistical comparison of survival with the comparators using the updated results, and considered that any survival advantage over the comparators will be reduced from that estimated using the first data cut.

7.6 The PBAC noted the claim of superior comparative effectiveness to all the nominated comparators was based on indirect comparisons. The PBAC noted and accepted that PFS and OS outcomes for comparisons of ibrutinib (RESONATE-2) and ritux+chl (CLL11) and ofa+chl (COMPEMENT-1) indicated the superior effectiveness of ibrutinib. The PBAC considered the magnitude of long-term benefit was uncertain because of the indolent nature of the disease and hence the small number of clinical events observed in the trials, in particular for ibrutinib with only 18 months follow-up for the RESONATE-2 trial. The PBAC considered that the additional follow-up to 44 months in the Phase 1b/2 studies for 27 treatment-naïve patients presented in the pre-PBAC response (p1) was insufficient evidence to support the sustained benefit of first-line ibrutinib.

7.7 The PBAC noted the results of the indirect comparison of ibrutinib (RESONATE-2) with obi+chl (CLL11) showed there was no statistically significant advantage for ibrutinib in terms of PFS or OS compared to obi+chl. The PBAC noted the submission considered that due to differences in chlorambucil dosing in RESONATE-2 and CLL11, the indirect comparisons were biased against ibrutinib. The PBAC noted that although different dosing schedules were allowed, the median time on treatment was similar (7.1 months in RESONATE-2 vs 5.5 months in CLL11). Additionally, the median investigator-assessed PFS for the chl arms were not substantially different (15 months in RESONATE-2 vs 11.1 months in CLL11). The PBAC therefore considered the that variations in chlorambucil dosing when used as a common comparator was not a significant issue nor sufficient justification to rely on a single arm comparison in preference to an indirect comparison based on randomised trials. Thus, the PBAC advised that the claim of superior comparative effectiveness compared to ob+chl was not adequately supported.

7.8 The PBAC considered the claim of non-inferior safety to the comparators was supported by the indirect comparisons, but reiterated its concerns that ibrutinib is associated with an increased risk of clinically significant atrial fibrillation. The PBAC also noted the increased risk of bleeding with ibrutinib, and was concerned that incidence of bleeding in the proposed PBS population would be higher than in the RESONATE-2 trial, given the stringent exclusion criteria of patients at high bleeding risk in the trial.

7.9 The PBAC considered the economic model unreliable and the resulting ICER to be high and optimistic, given the extrapolation of immature clinical trial data to a 20-year time horizon for patients >70 years of age who will likely have comorbidities, and the assumed high magnitude of clinical benefit over obi+chl. The PBAC agreed with the ESC that, on the basis of the available evidence, a more informative

approach to assessing the cost-effectiveness of ibrutinib in the first-line setting would be a CUA vs ritux+chl with a comparable ICER to obi+chl vs ritux+chl from March 2015 ($15,000/QALY - $45,000/QALY) or a CMA vs obi+chl. The PBAC noted the ICER accepted for ibrutinib in R/R CLL was $45,000/QALY - $75,000/QALY gained, when the OS curves converged at 10 years. The PBAC acknowledged that a CMA would be difficult for estimating treatment duration given the immature PFS data from RESONATE-2. However, the option of CUA over ritux+chl with a 10-year time horizon could be used to establish a cost-effective price, as was accepted for obi+chl in March 2015.

7.10 The PBAC noted the DUSC advice that the high, uncertain and likely under-estimated financial impact of first-line listing of ibrutinib was driven by the failure to include prevalent patients, and the uncertain treatment duration and sequencing which was based on the economic model. The PBAC noted and welcomed the pre-PBAC response (pp3-4) acknowledging the uncertain financial impact, and agreed in principle with the proposal from the sponsor to enter a risk share arrangement for CLL as a whole, combing first-line and R/R CLL in the unfit patient population.

7.11 The PBAC considered a major resubmission would be required, and should include the following:

- a definition of inappropriate for fludarabine-based therapy in the proposed restriction;
- updated PFS and OS data if available from the RESONATE-2 trial;
- a revised economic analysis based on a CUA vs ritux+chl with a 10-year time horizon, with an ICER under $45,000/QALY - $75,000/QALY gained (consistent with the accepted ICERs for obi+chl in first-line CLL, and less than ibrutinib in R/R CLL to take into account the high uncertainty regarding long-term incremental benefit);
- revised financial estimates based on updated estimates of the likely incident and prevalent population, and a revised RSA proposal that accounts for the uncertainty in the patient population and estimated duration of therapies.

7.12 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

Janssen will continue to work with the PBAC to make ibrutinib available to patients as soon as practical.