

5.07 IBRUTINIB, oral capsule, 140mg, Imbruvica[®], Janssen-Cilag Pty Ltd.

1 Purpose of Application

- 1.1 The submission requested Section 85, Authority Required listing for ibrutinib for the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL).

2 Requested listing

- 2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
IBRUTINIB Capsule 140 mg	3	5	Published \$ [REDACTED] Effective \$ [REDACTED]	Imbruvica Jansen

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Relapsed or refractory chronic lymphocytic leukaemia
Restriction Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	The patient must have received at least one prior therapy <i>for this indication</i> AND The patient must be considered unsuitable for treatment or retreatment with a purine analogue AND Patient must have a WHO performance status score of less than 2 AND Patient must not receive PBS-subsidised ibrutinib if progressive disease develops while on PBS-subsidised ibrutinib.
Prescriber Instructions	<i>Treatment must be discontinued in patients who experience disease progression while on treatment</i>

Public Summary Document – July 2015 PBAC Meeting

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Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Relapsed or refractory small lymphocytic lymphoma
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	The patient must have received at least one prior therapy <i>for this indication</i> AND The patient must be considered unsuitable for treatment or retreatment with a purine analogue AND Patient must have a WHO performance status score of less than 2 AND Patient must not receive PBS subsidised ibrutinib if progressive disease develops while on PBS subsidised ibrutinib.
Prescriber Instructions	<i>Treatment must be discontinued in patients who experience disease progression while on treatment</i>

- 2.2 ESC noted there is considerable risk of usage outside the requested listing given that the TGA-approved indication for ibrutinib was not restricted to patients unsuitable for treatment with a purine analogue (i.e. fludarabine). Further, the results of the HELIOS trial indicated that there is a significant benefit from adding ibrutinib to immunochemotherapy (specifically bendamustine plus rituximab). The Pre-Sub-Committee Response (PSCR) acknowledged this risk and stated that the sponsor was willing to negotiate both the restriction and a risk-sharing arrangement. The PSCR proposed that a Telephone Authority could mitigate the risk of use in patients suitable for treatment with fludarabine
- 2.3 The submission stated that currently approximately [REDACTED] patients receive ibrutinib through the Named Patient Program. These patients were recruited using the inclusion and exclusion criteria of the key clinical trial, which was in line with the proposed restriction. The PSCR provided information on these criteria.
- 2.4 The submission presented a cost-utility analysis of ibrutinib compared with rituximab plus chlorambucil.

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

3 Background

- 3.1 **TGA status at time of PBAC consideration – from ARTG certificate:** Ibrutinib was registered in April 2015 for the treatment of patients with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) who have received at least one prior therapy or as first line in patients with CLL with 17p deletion; and patients with mantle cell lymphoma who have received at least one prior therapy.
- 3.2 However, the current submission did not seek listing in the following indications:
- first-line use in patients with CLL with 17p deletion, and
 - mantle cell lymphoma (awaiting results of a phase III comparative trial).
- Further, the TGA-approved indication allows use of ibrutinib in patients who are suitable for treatment with a purine analogue (i.e. fludarabine).
- 3.3 The item had not been considered by the PBAC previously. At the March 2015 PBAC meeting:
- the PBAC did not recommend the listing of idelalisib for the treatment of patients with CLL because the patient population was not adequately defined, the nominated comparator was inappropriate, and the economic evaluation required amendment. Therefore the cost-effectiveness could not be estimated, in the context of a drug with a high cost compared with current care; and
 - obinutuzumab (given with chlorambucil) was recommended for listing on the PBS as a first-line treatment option for patients with CLL who are unfit with comorbidities.
- 3.4 Ofatumumab in combination with chlorambucil is PBS listed for first-line treatment of CLL for patients inappropriate for treatment with fludarabine.

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

4 Clinical place for the proposed therapy

- 4.1 Ibrutinib was evaluated as a treatment for patients with relapsed or refractory CLL/SLL, which are haematological B-cell malignancies.
- 4.2 ESC noted the clinical evidence provided by the submission, the proposed TGA indication and the proposed PBS restriction, suggested that ibrutinib would be used for patients with relapsed/refractory CLL/SLL deemed unfit for further treatment with a purine analogue (i.e. fludarabine). However, the TGA-approved indication for ibrutinib does not require patients to be considered unsuitable for treatment with fludarabine and allows for treatment for first-line patients with CLL with 17p deletion.

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

5 Comparator

- 5.1 Rituximab plus chlorambucil (Rit+Chl). This was appropriate, for the proposed restriction. However, if ibrutinib would not be limited to those patients who are not

suitable for fludarabine treatment, fludarabine plus cyclophosphamide plus rituximab (FCR) might be the more appropriate comparator. The submission nominated idelalisib plus rituximab as a supportive comparator, as it was considered by the PBAC in March 2015. As idelalisib plus rituximab was rejected by the PBAC, this comparison was not evaluated in the commentary.

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 (29), health care professionals (3) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with ibrutinib including better survival, an improved quality of life, improved tolerance compared to standard chemotherapy, less hospitalisation and fewer infections.

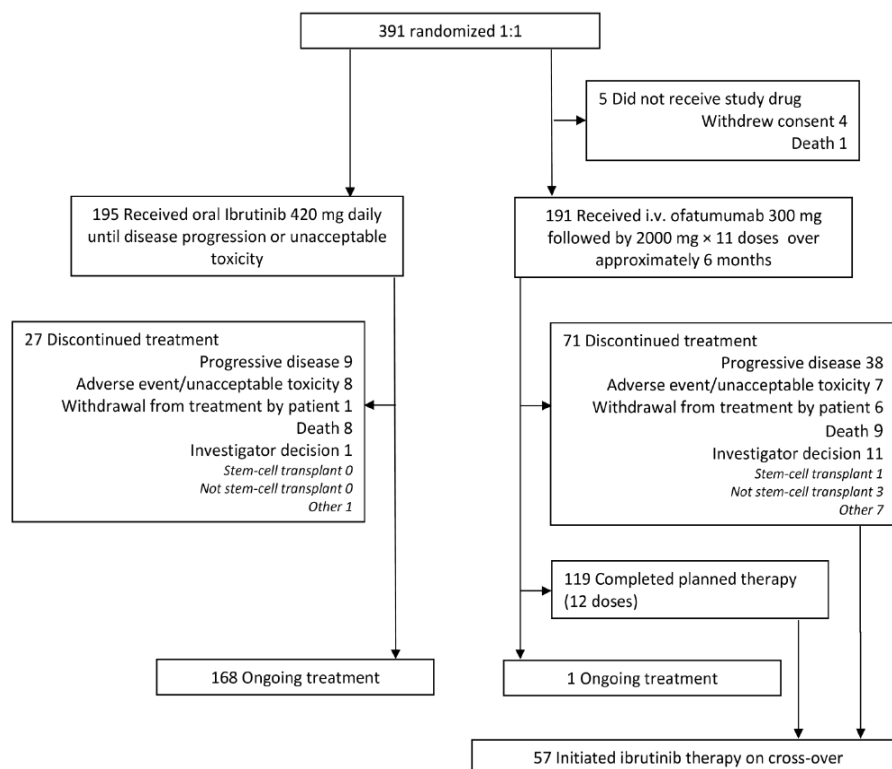
6.3 The PBAC noted the advice received from Lymphoma Australia clarifying the likely use of ibrutinib in clinical practice. The PBAC specifically noted the advice that around 1,200 patients are diagnosed with CLL/SLL each year and most of these patients are over 55 years of age, the use of ibrutinib may be superior to standard, approved treatments for some CLL/SLL patients, the availability of ibrutinib in tablet form has positive psychological effects for patients from less travel time to seek treatment and cost to receive treatment in this form and that the side effects associated with this treatment are considered manageable by patients. The PBAC noted that this advice was supportive of the submission.

Clinical trials

6.4 The submission was based on one head-to-head trial comparing ibrutinib to ofatumumab, RESONATE (n=391). The submission provided two different data-cuts from the RESONATE trial, the interim analysis and the longer-term analysis (median duration of follow up: 9.4 months and 16 months, respectively). Data from the pre-specified interim analysis is presented in the clinical claim of the commentary. At the interim analysis, progression free survival was assessed by the Independent Review Committee, while at the ad-hoc longer term analysis progression free survival was assessed by the investigator. Further, a protocol amendment occurred approximately four months after the last patient was randomised. This was due to promising data from a phase 2 study. This protocol amendment allowed patients in the ofatumumab arm who had disease progression, as assessed by the Independent Review Committee, to receive ibrutinib. After the interim analysis, all patients in the ofatumumab arm were allowed to switch to ibrutinib treatment. A total of 29% of patients switched from ofatumumab to ibrutinib within the interim analysis, increasing to 61% in the longer-term ad-hoc analysis. The economic evaluation relied on data

from the longer-term ad hoc analysis. Figure 1 presents the patient flow through the interim analysis of the RESONATE trial.

Figure 1: Patient flows through the RESONATE trial (interim analysis)



Source: Figure Bi.2, p64 of the submission

- 6.5 The submission provided no direct evidence to support the claim that ofatumumab would be non-inferior to rituximab plus chlorambucil. In the absence of evidence the sponsor assumed that ofatumumab was of equivalent efficacy to rituximab plus chlorambucil. The sponsor noted that the PBAC (November 2014), on the basis of the results of an indirect comparison, considered that ofatumumab plus chlorambucil was non-inferior to rituximab plus chlorambucil in the treatment of previously untreated patients with CLL. The submission proposed that it was reasonable to also assume non-inferiority of ofatumumab versus rituximab plus chlorambucil in the relapsed/refractory setting. ESC considered that there was no basis to assume that ofatumumab monotherapy would have a similar efficacy to ofatumumab with the addition of chlorambucil.
- 6.6 Additionally, the submission provided evidence of safety in the form of comparing the ofatumumab results from the key trial with safety results from a single arm, open-label, phase 2 study where rituximab plus chlorambucil was provided to CLL patients in the first-line setting (Hillmen 2014; n=100).
- 6.7 ESC considered that the results from Österborg et al. (2014) presented in the PSCR provided limited evidence to support the claim that the efficacy of ofatumumab is at least no worse than Rit+Chl. No details were provided on the baseline characteristics

of the trial participants, the number of participants using rituximab plus an alkylator was small (n=12) and the results for this subgroup were not presented.

- 6.8 An open-label phase 2 study (Tam et al., 2014), comparing second-line treatment after FCR treatment, was presented in the submission to compare the predicted overall survival from the ofatumumab arm in the RESONATE trial with long-term survival observed in relapsed/refractory CLL patients treated with rituximab. The patient population in Tam (2014) who received rituximab based regimen was not comparable to the patients included in the RESONATE trial. ESC agreed with the Commentary and the PSCR that comparison with the Tam et al. (2014) cohort was inappropriate as the Rit+Chl regimen was not included in the trial.
- 6.9 Details of the trials presented in the submission are provided in Table 1.

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial ibrutinib vs. ofatumumab		
RESONATE	A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (PCYC-112-CA). Byrd JC, Brown JC, O'Brien S et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia.	Clinical Study Report. 01 March 2012 N Engl J Med (2014); 371 (13):213-223
Supportive studies rituximab and rituximab plus chlorambucil		
Tam (2014)	Tam, CS, O'Brien SO, Plunkett W et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukaemia.	Blood 2014;124(20):3059-64
Hillmen (2014)	Hillmen, P, Gribben JG, Follows GA et al. Rituximab plus chlorambucil as first-line treatment for chronic lymphocytic leukaemia: Final analysis of an open-label phase II study.	J Clin Oncol (2014).32(12): 1236-1241

Source: Table Bi.5, p57 of the submission

The comparison to the Tam paper was conducted during the evaluation

- 6.10 The key features of the direct randomised trial in the submission are summarised in Table 2.

Table 2: Key features of the included evidence of the included trials

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Ibrutinib vs. ofatumumab						
RESONATE	391	R, MC, OL 9.4m follow-up ^a	Unclear	Relapsed/refractory CLL/SLL, not suitable for purine therapy	PFS, OS, ORR	Yes
Rituximab + chlorambucil studies						
Hillmen 2014	100	Single arm, OL, 30 m follow-up ^a	High	First-line treatment CLL	Safety	No
Rituximab based regimens studies (excludes any combination with chemotherapy such as chlorambucil)						
Tam 2014	31	OL, 142 m follow-up ^a	High	CLL patients who failed FCR and were provided with rituximab based regimen ^b as 2 nd line treatment	OS, ORR	No

Source: compiled during the evaluation

FCR = fludarabine, cyclophosphamide, rituximab; m = months; MC = multi-centre; OL=open label; ORR = overall response

rate; OS = overall survival; PFS = progression free survival; R=randomised; CLL = chronic lymphocytic leukaemia; SLL = small lymphocytic lymphoma.

^a Median

^b Rituximab based regimens included rituximab monotherapy (n=11), rituximab plus methylprednisolone (n=10), rituximab plus granulocyte macrophage colony-stimulating factor (n=9) and rituximab plus etanercept (n=1).

Comparative effectiveness

- 6.11 Results of the primary outcome, progression free survival (as assessed by the Independent Review Committee) for the RESONATE trial are presented in Table 3.

Table 3: Progression free survival results and Kaplan-Meier estimates for RESONATE trial (ITT) – interim analysis, median follow-up 9.4 months

	Ibrutinib (n=195)	Ofatumumab (n = 196)	Hazard ratio (95% CI)
PFS ^a , patients with events, n/N (%)	35/195 (17.9%)	111/196 (56.6%)	0.22 (0.15, 0.32)
Median PFS; months (range)	NE (0.03, 13.96)	8.1 (0.03, 13.77)	-

Source: Table Bi.27, p87 of the submission

CI = confidence interval; ITT = intention-to-treat; NE = not estimable; PFS = progression free survival; **bold** = statistically significant

^a PFS for the interim analysis was assessed by the Independent Review Committee

- 6.12 Ibrutinib treatment resulted in significantly longer progression free survival than ofatumumab in patients with CLL/SLL, with a hazard ratio of 0.22 (95% confidence interval (CI): 0.15 to 0.32).

- 6.13 The results for overall survival and overall response rates based on interim data from the RESONATE trial and Tam (2014) are presented in Table 4.

Table 4: Results for the naïve comparison between ibrutinib and rituximab based regimens

	RESONATE – interim analysis		Tam (2014)
	Ibrutinib (n=195)	Ofatumumab (n = 196)	Rituximab based regimen ^a (n=31)
Median duration of follow-up	9.4 months	9.4 months	63 months ^b
OS; patients died	16/195 (8.2%)	33/196 (16.8%)	NR
Median OS; months	NE (■■■■, ■■■■)	NE (0.07, ■■■■)	36 months (NR, NR)
HR (95% CI)	0.43 (0.24, 0.79) - crossover censored 0.39 (0.22,0.70) – crossover not censored		NE
ORR; %	42.6% ^c 69.7% ^d	4.1% ^c 21.4% ^d	48.3% ^{d,e}

Source: Table Bi.30, p93; Table Bi.31-32, p99 of the submission, and extracted from Tam (2014)

FCR = fludarabine, cyclophosphamide, rituximab; NE = not estimable; NR = not reported; ORR = overall response rate; OS = overall survival; CI = confidence interval; HR = hazard ratio

^a Rituximab based regimens included rituximab monotherapy (n=11), rituximab plus methylprednisolone (n=10), rituximab plus granulocyte macrophage colony-stimulating factor (n=9) and rituximab plus etanercept (n=1).

^b This follow-up was for all patients on second-line therapy (n=136) in Tam (2014), as no data was provided for patients on a rituximab-based regimen.

^c Independent review committee assessed.

^d Investigator assessed.

^e Values were provided separately for patients who had a relapse less than 3 year (45%, n=11) after start of FCR treatment and those with relapse at least 3 year after start of FCR treatment (50%, n=20).

- 6.14 Like the hazard ratio for overall survival, when patients who crossed over were censored in the interim phase of the RESONATE trial, the uncensored hazard ratio was 0.39 (95% CI: 0.22 to 0.70) and favoured ibrutinib over ofatumumab. The

median overall survival was not reached in either treatment arm due to a low event rate. Tam (2014) reported that the median overall survival for rituximab based regimens in patients who failed FCR was 36 months (no confidence intervals provided). Overall, meaningful comparisons of efficacy between ofatumumab and rituximab plus chlorambucil cannot be made. ESC agreed that ibrutinib appears to be superior to ofatumumab based on the RESONATE trial. However, it is not clear whether the treatment effect in comparison to ofatumumab is a reasonable estimate of the benefit over Rit+Chl. ESC noted that the use of single agent anti-CD20 therapy, such as ofatumumab and rituximab, generally results in poor and short-lived responses in relapsed/refractory CLL. ESC considered that the addition of chlorambucil to anti-CD20 therapy would likely have greater efficacy than single agent anti-CD20 therapy alone. As such, the estimated benefit for ibrutinib was considered to have been overestimated when based on a comparison to ofatumumab as monotherapy.

- 6.15 Ibrutinib treatment resulted in a higher response rate than ofatumumab treatment. For both treatment arms in the RESONATE trial, the overall response rates were lower when the assessment was done independently then when done by the investigator. Further, the overall response rate in the ofatumumab arm of RESONATE was much lower than that reported in the rituximab based regimens of Tam (2014) or in patients treated with ofatumumab who failed fludarabine and alemtuzumab which was 47% (95% CI: 39% to 60%) (Ofatumumab Australian product information, p7).

Comparative harms

- 6.16 The most common treatment-related adverse events Grade 3 or higher across both trial arms were neutropenia, pneumonia, thrombocytopenia and anaemia. Urinary tract infections, leucocytosis, atrial fibrillation and lung infection were reported more often in the ibrutinib arm, with infusion-related reactions reported more often in the ofatumumab trial arm.
- 6.17 The submission did not present direct comparative safety results for ibrutinib and rituximab plus chlorambucil. However, the submission did provide a naïve comparison of safety for ofatumumab from the RESONATE trial to rituximab plus chlorambucil for first-line treatment for CLL (Hillmen, 2014). The submission concluded that the safety profiles were largely similar. This was inappropriate as the comparison was for different lines of treatment and the median follow-up was 30 months for Hillmen (2014), whereas the median follow-up for the RESONATE trial was 9.4 months.

Benefits/harms

- 6.18 Ibrutinib versus ofatumumab
A summary of the comparative benefits and harms for ibrutinib versus ofatumumab is presented in Table 5.

Table 5: Summary of comparative benefits and harms for ibrutinib and ofatumumab

BENEFITS						
Interim analysis: RESONATE trial – crossover censored						
Progression free survival (Median duration on treatment: ibrutinib = 8.6 months; ofatumumab = 5.3 months)						
	Ibrutinib	Ofatumumab	Absolute Difference	HR (95% CI)		
Progressed disease; n/N (%)	35/195 (17.9%)	111/196 (56.6%)	-38.7% (-47.5, -29.9)	-		
Median; months	NE	8.1 months	-	0.22 (0.15, 0.32)		
Overall survival (Median duration on treatment: ibrutinib = 8.6 months; ofatumumab = 5.3 months)						
Died; n/N (%)	16/195 (8.2%)	33/196 (16.8%)	-9% (-15.1, -2.1)	-		
Median; months	NE (■■■■, ■■■■)	NE (■■■■, ■■■■)	-	0.43 (0.24, 0.79)		
Longer-term analysis: Ad hoc – crossover uncensored						
Overall survival: (Median duration on treatment: ibrutinib = 16 months; ofatumumab = 5 months)						
Died; n/N (%)	■■■■ (■■■■%)	■■■■ (■■■■%)	- % (-■■■, -■■■)	-		
Median; months	-	-	-	■■■■ (■■■■, ■■■■)		
Interim analysis: RESONATE trial						
HARMS – Grade 3/4						
	Ibrutinib	Ofatumumab^a	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Ibrutinib	Ofatumumab	
UTI; n/N	7/195	1/191	6.86 (0.85,55.20)	3.6	0.5	3.1% (0.3, 5.9)^b
Leukocytosis; n/N	6/195	0	NC ^b	3.1	0	3.1 (0.7, 5.5)^b
Atrial fibrillation; n/N	6/195	0	NC ^b	3.1	0	3.1% (0.7, 5.5)^b
Lung infection; n/N	5/195	0	NC ^b	2.6	0	2.6% (0.3, 4.8)^b
Infusion reaction n/N	0/195	6/191	NC ^b	0	3.1	-3.1% (-5.6, -0.7)^b

Source: Table Bi.27, p87; Table Bi.30, p93; Table Bi.52, p124 of the submission, and p4, Ad-Hoc CSR provided with the submission

CI = confidence interval; HR = hazard ratio; NC = not calculable; NE = not evaluable; RD = risk difference; RR = relative risk; UTI = urinary tract infection; **bold** = statistically significant

* Median duration of follow-up 9.4 months

^a Five patients randomised to ofatumumab did not receive treatment

^b Submission presented different estimates

- 6.19 Median progression free survival and overall survival was not reached for ibrutinib, whereas median progression free survival was approximately 8.1 months for ofatumumab with median overall survival not reached.

On the basis of direct comparison evidence presented by the submission, for every 100 patients treated with ibrutinib in comparison to ofatumumab, over a 9.4 month median duration of follow-up, there were approximately three additional Grade 3 or 4: urinary tract infections; lung infections; leucocytosis; and atrial fibrillation events. There were approximately three fewer Grade 3 or 4 infusion-related reactions. The naïve comparison presented by the submission was not appropriate to allow a comparison between ibrutinib and rituximab plus chlorambucil.

Clinical claim

- 6.20 Ibrutinib versus ofatumumab
The submission described ibrutinib as superior in terms of comparative effectiveness, and as different in terms of comparative safety, compared to ofatumumab for patients with relapsed or refractory CLL/SLL.

6.21 This claim of superior comparative effectiveness of ibrutinib over ofatumumab monotherapy was based on the data from the RESONATE trial for patients with relapsed or refractory CLL. Ibrutinib showed superior progression free survival and overall survival benefits compared to ofatumumab. However the evaluation noted several concerns with this conclusion:

- The generalisability of the RESONATE trial results is questionable given the TGA-approved indication for ibrutinib is not restricted to patients unsuitable for treatment with a purine analogue (i.e. fludarabine);
- The claim of superiority was only considered valid if ofatumumab monotherapy was considered as an appropriate clinical comparator;
- The design of the RESONATE trial resulted in substantial cross-over which makes the longer term follow-up uncertain. A protocol amendment was approved four months after the last patient was randomised. This amendment allowed ofatumumab patients to crossover to ibrutinib upon disease progression, as assessed by an Independent Review Committee. This resulted in 29% of the ofatumumab patients to crossover to ibrutinib; and
- the efficacy of ofatumumab in the RESONATE trial might have been underestimated, as the Independent Review Committee reported response rate was 4%, well below response rates reported for other treatments used in the relapsed/refractory setting, e.g. in the Study 116 idelalisib trial the overall response rate for rituximab monotherapy was reported to be 13%.

6.22 The claim of different comparative safety might be supported as:

- ibrutinib was associated with higher rates of Grade 3 or 4 urinary tract infections, leucocytosis, atrial fibrillation and lung infections, while ofatumumab was associated with higher rates of Grade 3 or 4 infusion-related reactions. However, the confidence intervals for risk difference were wide (due to low event rates) for urinary tract infection, leucocytosis, atrial fibrillation and lung infection.
- The duration of treatment of ofatumumab might reflect clinical practice as the maximum duration of treatment is 12 doses over a 6-month period, while the duration of ibrutinib might not reflect clinical practice as treatment can continue until disease progression or toxicity. This could potentially result in an inferior safety claim.

6.23 Ibrutinib versus rituximab plus chlorambucil

The submission described ibrutinib as superior in terms of comparative effectiveness, and as different in terms of comparative safety, compared to rituximab plus chlorambucil for patients with relapsed or refractory CLL/SLL.

The claim made by the submission that ibrutinib was superior to rituximab plus chlorambucil was not supported. The submission did not provide direct evidence between ibrutinib and rituximab plus chlorambucil. The claim assumes that ofatumumab monotherapy is equivalent in effectiveness to the combination of rituximab plus chlorambucil. ESC considered that the comparison of ibrutinib vs. ofatumumab was likely to have overestimated the benefit of ibrutinib over the combination of rituximab plus chlorambucil (to an unknown degree) given that the addition of immunochemotherapy is generally more effective than anti-CD20 monotherapy for individuals with relapsed/refractory CLL.

- 6.24 The submission provided a naïve comparison of the toxicity of ofatumumab from the RESONATE trial (median follow-up: 9.4 months) and study by Hillmen (2014). This latter study provided safety outcomes of a first-line study of patients treated with rituximab plus chlorambucil with a median follow-up of 30 months.

Economic analysis

- 6.25 The submission presented a stepped economic evaluation (cost-utility analysis) for the comparison of ibrutinib with rituximab plus chlorambucil (Table 6). The submission used the longer-term ad-hoc data from the RESONATE trial to estimate progression free survival and overall survival in the economic model.

Table 6: Summary of model structure and rationale

Time horizon	20 years in the model base case vs. a median duration of follow-up of 9.4 months at the interim analysis.
Outcomes	LYG and QALYs
Methods used to generate results	Trial based; Markov model; cohort expected value analysis; deterministic sensitivity analysis
Health states	Alive with progression free disease; alive with progressed disease; dead
Cycle length	30 days
Transition probabilities	Based on Kaplan-Meier curves for progression free survival and overall survival and extrapolation of these curves. The KM curves were from the longer term follow-up where a large proportion of the ofatumumab patients had crossed over to ibrutinib. The submission assumed convergence of overall survival, starting after 2 years, with full convergence at 25 years. The convergence was incorrectly calculated in the economic model. This was updated during evaluation.

Source: compiled during the evaluation

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

- 6.26 The time horizon and the model structure were the key drivers of the model, and appeared to favour ibrutinib (Table 7). The modelling structure assumption that convergence would occur at 25 years was not consistent with the PBAC's previous preference for convergence at 10 years for rituximab plus chemotherapy (November 2010). The assumption of a continuing treatment effect, although diminishing over time, was not justified.

Table 7: Key drivers of the model

Description	Method/Value	Impact
Efficacy Rit + Chl	Assumed that ofatumumab from RESONATE would be the same as rituximab plus chlorambucil.	Unclear, favoured ibrutinib
Time horizon	20 years; assumed from mean [redacted] months trial duration	High; favoured ibrutinib
Model structure	25 year convergence of overall survival benefit of ibrutinib	High; favoured ibrutinib
	3-state model without additional lines of treatment or cost of living with progressed disease	Unclear
Resource use/costs	MBS and AR-DRG costs; trial-based	Low; favoured ibrutinib

Source: compiled during the evaluation

MBS = Medicare Benefits Schedule; AR-DRG = Australian refined diagnosis-related group; Rit + Chl = rituximab plus chlorambucil

- 6.27 The PSCR argued that the submission's selection of a 20 year time horizon was supported by AIHW (2014) CLL survival data where 18.9% of patients are expected to survive after 20 years from diagnosis. The sponsor further argued that based on

the PBAC Guidelines the appropriate time horizon is lifetime and therefore a 20 year duration was a reasonable upper limit for the economic modelling (PSCR). ESC did not agree with response and considered that the assumption of 20 years is not an appropriate time horizon for the intended PBS population. It was not in line with previous PBAC recommendations of a 10 year horizon for the CLL population involving older persons with other comorbidities. ESC noted that the CLL survival figures sourced from the AIHW included individuals who were untreated and unfit and therefore were not fully representative of the proposed PBS population.

- 6.28 The results of the economic evaluation are presented in Table 8. The model was corrected during evaluation for a mathematical error with regards to the convergence rate.

Table 8: Results of the stepped economic evaluation

Step and component	Ibrutinib	Rituximab plus chlorambucil	Increment
Step 1-2: trial-based economic evaluation (undiscounted)			
Cost	\$ [redacted]	\$ [redacted]	\$ [redacted]
LYs	[redacted]	[redacted]	[redacted] ^a
QALYs	[redacted]	[redacted]	[redacted] ^a
Incremental cost per LY gained (undiscounted)			\$ [redacted]
Incremental cost per QALY gained (undiscounted)			\$ [redacted]
Step 3: modelled economic evaluation (discounted) extrapolated after 16 m (ibr) and 12m (rit + chl) to 20 y			
Cost	\$ [redacted]	\$ [redacted]	\$ [redacted]
LYs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost per LY gained			\$ [redacted]
Incremental cost per QALY gained			\$ [redacted]
Base case (Step 4) assuming diminishing treatment benefit for ibrutinib beyond the RESONATE trial			
Cost	\$ [redacted]	\$ [redacted]	\$ [redacted]
LYs	[redacted]	[redacted]	[redacted] (submission) [redacted] (corrected) ^b
QALYs	[redacted]	[redacted]	[redacted] (submission) [redacted] (corrected) ^b
Incremental cost per LY gained			\$ [redacted]
Incremental cost per QALY gained			\$ [redacted] ^b

Source: Table D.3, Table D.4 p257; Table D.5, p258; Table D.6, p261 of the submission

AE = adverse event; LY = life year; m = months; QALY = quality-adjusted life year; y = years; rit + chl = rituximab plus chlorambucil

^a Differences in incremental value compared to the treatment values were due to rounding

^b Corrected values for the mathematical error in applying the convergence factor in the economic model

- 6.29 The economic evaluation resulted in an incremental cost-effectiveness ratio (ICER) of \$45,000 - \$75,000 (\$45,000 - \$75,000, corrected for a mathematical error) per quality-adjusted life year (QALY) for ibrutinib versus rituximab plus chlorambucil. The ICER was uncertain due to:

- the appropriateness of the use of the RESONATE trial to estimate the clinical efficacy:
 - trial duration was short compared to the model duration;
 - efficacy of ofatumumab might have been underestimated, due to trial design (open-label). The reported response rate was lower than response rates reported in the literature for second-line treatments (e.g. 13% for rituximab monotherapy in Study 116 (idelalisib trial)); and

- evidence presented in the submission did not support that rituximab plus chlorambucil was equivalent to ofatumumab in terms of efficacy and safety.
 - the time horizon was 20 years. This was longer than the 10 year time horizon which the PBAC considered appropriate for CLL patients who are older and have other comorbidities (rituximab public summary document March 2010). This longer time horizon favoured ibrutinib;
 - the exponential extrapolation of overall survival in the model beyond the trial duration did not fit the trial best by Akaike information criteria, as the submission excluded the lognormal and gamma distribution from its consideration. The submission excluded these models, as it would not reflect long-term overall survival. While this was correct, it might have been more appropriate to include the best fitting model as well as mortality due to non-CLL causes to better reflect overall survival in this patient group. Therefore, a model better reflecting clinical practice could include gamma extrapolation and apply Australian all-cause mortality rates. The PSCR argued that the gamma extrapolation was excluded as it was considered to overestimate survival and that the exponential function was used in the base case model as it gave an appropriate projection of survival. The PSCR considered that the modelling captures the necessary impacts of all cause mortality from the trial data. However, there was only 9 months of trial data which may not reflect the all-cause mortality rate over the full time horizon of the model. Overall, ESC considered that the larger issue was the assumption of a 20 year time horizon rather than the method of extrapolation that was used;
 - the convergence of effect of ibrutinib with ofatumumab which was applied at 25 years; which is longer than that recommended by the PBAC for rituximab plus chemotherapy (i.e. 10 year). This structural assumption favoured the overall survival gain seen in ibrutinib;
 - the three-state model used to estimate the cost and benefits did not reflect long term clinical practice of patients with CLL/SLL where most patients would be expected to receive more than two lines of treatment. A three-state model did not reflect treatment benefits and costs for future lines of treatment. An appropriate model structure would include progressed disease without treatment and progressed disease with further treatment. The PSCR argued that the structure reflects that patients are in a salvage treatment setting and that the structure was based on clinical expert advice. However, ESC considered that the model was unlikely to reflect all the treatment options available or the indolent nature of the disease; and
 - the submission did not include health state costs, which was inappropriate and was likely to favour ibrutinib as patients lived longer and would therefore have longer term healthcare costs.
- 6.30 The submission presented univariate sensitivity analyses, which indicated that the model was most sensitive to the price of ibrutinib, time horizon and convergence of overall survival benefit (Table 9). The following issues were not tested in sensitivity analyses during evaluation: 1) use of interim analyses of the RESONATE trial; 2) other methods of extrapolation of overall survival; 3) additional health states post progression; and 4) inclusion of health state costs. All analyses were updated to include the correction for the convergence factor.

Table 9: Results of key univariate and multivariate sensitivity analyses (discounted) – updated for mathematical error in convergence factor

Univariate analyses	Inc. costs	Inc. effectiveness	Inc. CE
Base case (submission)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Base case – corrected for convergence error	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Time horizon (base case = 20 years)			
5 years ^c	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
10 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
15 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Extrapolation: no convergence of overall survival (base case = after 25 year)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Time point for convergence (base case = end trial follow-up)			
5 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
10 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Convergence at 10 year ^c			
Start convergence 2 year ^a	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Start convergence 5 year ^b	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Multivariate analyses^c			
10 year time horizon, convergence start after 2 year and full convergence at 10 year	\$ [REDACTED]	0.72	\$ [REDACTED]
10 year time horizon, convergence start after 5 year and full convergence at 10 year	\$ [REDACTED]	0.89	\$ [REDACTED]

Source: Table D.7, p263 of the submission.

CE = cost-effectiveness; DPMQ = dispensed price for maximum quantity; Inc = incremental

^a The reduction in parameter Cell I12 was multiplied by 2.9

^b The reduction in parameter Cell I11 was multiplied by 3.9

^c Compiled during evaluation

6.31 In the Pre-PBAC response, the sponsor presented a re-specified ICER (\$45,000 – \$75,000 per QALY) based on an overall survival estimate that had been adjusted for patient cross-over in the RESONATE trial. The PBAC noted the sponsor’s argument that the intention-to-treat (ITT) overall survival results were potentially biased towards the null by not accounting for an additional survival gain in the comparator arm from treatment with ibrutinib. Using the Rank Preserving Structural Failure Time Model (RPSFTM), the Pre-PBAC response reported an adjusted hazard ratio of [REDACTED].

Drug cost per patient per course: \$ [REDACTED]

6.32 The drug cost per patient per course was based on mean duration of treatment from the RESONATE trial of [REDACTED] months, an effective dispensed price of maximum quantity (DPMQ) of \$ [REDACTED] and a dose intensity of [REDACTED]%. The treatment time for ibrutinib in clinical practice could be longer, with an associated higher cost due to the median progression free survival not reached within the RESONATE trial. This was compared to \$ [REDACTED] for rituximab plus chlorambucil, over mean duration of 6 months, using the December 2014 listed price for rituximab.

Estimated PBS usage & financial implications

- 6.33 This submission was considered by the Drug Utilisation Sub-Committee (DUSC). The net cost to the Government of listing ibrutinib was estimated in the submission to be more than \$100 million dollars over the first five years. This cost was expected to peak at \$60 – 100 million in Year 3. The financial estimates may be underestimated as:
- there may be use beyond the proposed PBS restriction. The main TGA approval is for second-line treatment, while the proposed restriction further limited to patients for whom fludarabine is considered inappropriate;
 - There is limited evidence to derive estimates of patient numbers, i.e. the uptake rates were based on a small survey of haematologists, with insufficient information provided in the submission to verify the assumptions;
 - the duration of treatment for ibrutinib could be longer than estimated by the submission as the mean treatment duration in the trial was ■■■ months but progression free survival was not reached indicating that time on therapy could be greater in practice; and
 - the cost offsets for rituximab plus chlorambucil might have been overestimated due to:
 - the maximum duration of treatment of rituximab (6 months) was used as opposed to the mean of 5.3 months; consistent with the same approach used to for ibrutinib;
 - the assumption that there would be cost offsets for grandfathered patients; and
 - ibrutinib would not be limited to monotherapy according to the TGA product information or proposed PBS restriction. This might result in potential co-administration of ibrutinib with rituximab, resulting in lower cost offsets.
- 6.34 DUSC noted the submission's incidence-based approach to derive the financial estimates did not account for the use of ibrutinib in patients diagnosed with CLL prior to 2012. DUSC considered that there would be a large prevalent group of CLL patients diagnosed prior to 2012 who may be treated with ibrutinib if it is listed on the PBS. The DUSC re-estimates indicate there may be less than 10,000 additional prevalent patients who may use ibrutinib on the PBS.
- 6.35 DUSC considered that the submission's estimate for the uptake of ibrutinib of ■■■% was too low for an efficacious oral treatment for patients with few other treatment options. DUSC considered that the uptake could reach ■■■% of the eligible population in the first 5 years of listing. In year 1, the cost to Government may be 6.5 times more than estimated in the submission. Overall, there may be an additional cost of more than \$100 million over the first 5 years of listing.
- 6.36 DUSC considered there to be a high likelihood of use outside of the restriction, particularly as an earlier line therapy in patients who are able to use purine analogues.
- 6.37 DUSC considered the ibrutinib restriction should define 'unsuitable for treatment or retreatment with a purine analogue', define progressive disease and prevent co-administration with rituximab.

Table 10: DUSC revised estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients starting ibrutinib	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Packs	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total net cost of ibrutinib to PBS/RPBS/MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Submission's estimates of patients starting ibrutinib	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Submission's estimated net cost of ibrutinib to PBS/RPBS/MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

The redacted table above shows that the estimated use and financial implications of ibrutinib to the PBS/RPBS/MBS for the treatment of CLL is less than 10,000 patients per year and \$10 - \$20 million in Year 1, \$30 – 60 million in Years 2, 4 and 5 and \$60 – 100 million in Year 3.

Quality Use of Medicines

6.38 The submission outlined the importance of the patients, prescribers and dispensers in assuring the appropriate use of ibrutinib. The submission stated that these groups would be provided with education, resources and support from the sponsor on the appropriate use of ibrutinib.

Financial Management – Risk Sharing Arrangements

6.39 The submission stated that the risk of leakage into other B-cell malignancies was low given:

- the standards of care are well-established whereas ibrutinib is yet to be established; and
- the prescribing rights limited to haematologists and medical oncologists.

6.40 The TGA-approved indication for ibrutinib is also recommended for first-line patients with CLL with 17p deletion and mantle cell lymphoma, which are not in the proposed PBS restriction. The TGA approved indication is broader than the proposed PBS listing, i.e. the TGA-approved indication is for CLL patients on second-line treatment, while the PBS listing would be confined to CLL patients with relapsed disease for whom fludarabine is considered inappropriate.

6.41 The submission stated that a risk share arrangement should be based upon an assumption of 100% uptake in eligible patients with an appropriate financial buffer before any rebates apply.

6.42 The PSCR acknowledged that there may be some risk that ibrutinib may be used in patients who are suitable for treatment with fludarabine. To reduce the risk of this occurring, the sponsor is willing to work with the Department to negotiate both the restriction and a risk-sharing arrangement.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of ibrutinib for the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL). In reaching this conclusion, the PBAC considered that the patient population and clinical place of ibrutinib were not adequately defined, the size of the comparative clinical benefit could not be quantified and the cost effectiveness and financial implications were underestimated and unacceptably high. The PBAC noted the main TGA approval is for second-line treatment of relapsed or refractory CLL and SLL, while the proposed restriction was further limited to patients for whom fludarabine is considered inappropriate. Usage of ibrutinib beyond restriction was a distinct possibility.
- 7.2 The PBAC welcomed the input received from consumers, organisations and health care professionals. The comments noted that ibrutinib was better tolerated than standard chemotherapy, prolonged survival and improved quality of life. The PBAC agreed that there was a clinical need for an effective treatment for patients with relapsed or refractory CLL and SLL. The PBAC considered that ibrutinib is an oral drug that provides an additional avenue of therapy for patients with relapsed CLL and SLL and the Committee noted that there is an active research and development program for additional treatments for CLL.
- 7.3 The PBAC noted that the TGA approved indication for ibrutinib included first line treatment of patients with CLL with 17p deletion; and patients with mantle cell lymphoma who have received at least one prior therapy. The PBAC noted the clinical need for an effective treatment for these patient populations.
- 7.4 The PBAC noted preliminary results of the HELIOS trial indicated that there is a significant benefit from adding ibrutinib to immunochemotherapy (specifically bendamustine plus rituximab), though these therapies are not listed for patients with relapsed/refractory CLL/SLL.
- 7.5 The PBAC considered that rituximab plus chlorambucil (Rit+Chl) was the appropriate comparator, for the proposed restriction. However, the choice of comparator in any future submission should be reassessed in regards to the clinical place where ibrutinib would be used. For example, if listing aligned with the TGA indication, fludarabine plus cyclophosphamide plus rituximab (FCR) may be the more appropriate comparator.
- 7.6 The PBAC considered that ibrutinib is an effective treatment, but the magnitude of the comparative efficacy over the nominated comparator was difficult to quantify.
- 7.7 The PBAC agreed with its ESC that there was insufficient evidence to support applying the treatment effect of ofatumumab monotherapy, in the pivotal RESONATE trial, as a proxy for the nominated comparator, Rit+Chl. In addition, the PBAC noted that the treatment benefit for ofatumumab in the RESONATE trial was lower than observed in other trials.
- 7.8 The PBAC noted the concerns with the generalisability of the RESONATE trial as outlined in paragraphs 6.14, 6.21 and 6.23. The PBAC considered that there was insufficient evidence to characterise the additional benefit of ibrutinib versus

RIT+CHL. The PBAC agreed with its ESC that basing the comparative effectiveness of ibrutinib against RIT+CHL on the results of the RESONATE trial would likely result in an overestimate given the lower than expected response rate for the ofatumumab arm that was observed in the trial.

- 7.9 The PBAC noted the naïve comparison that was conducted using data from RESONATE and Hillmen (2014) to assess the comparative safety for ibrutinib versus Rit+Chl, as outlined in paragraph 6.24. The PBAC considered this analysis was inappropriate as the comparison was for different lines of treatment (RESONATE was in the relapsed/refractory setting vs. Hillmen for Rit+Chl in first-line) and the median follow-up was 30 months for Hillmen (2014) compared to a median follow-up time of 9.4 months for the RESONATE trial.
- 7.10 The Pre-PBAC response presented an overall survival estimate which had been adjusted for patient cross over using the Rank Preserving Structural Failure Time Model (RPSFTM), estimating a hazard ratio of (■■■■). The PBAC was unable to assess the relevant assumptions in choosing the RPSFTM as a possible adjustment methodology and thus whether the assumptions underlying the RPSFTM method had been fulfilled. As such, the PBAC could not determine if the RPSFTM adjusted estimate of improved effect on overall survival was more or less biased than the unadjusted estimate. The PBAC considered this information and sensitivity analysis using different adjustment methods would be informative for any future reconsideration.
- 7.11 Overall, the PBAC considered the claim of ibrutinib as superior in terms of comparative effectiveness compared to rituximab plus chlorambucil for patients with relapsed or refractory CLL/SLL was not supported in the submission. The PBAC considered that the comparative safety of ibrutinib and rituximab plus chlorambucil could not be determined from evidence provided in the submission.
- 7.12 The PBAC noted the issues with the economic evaluation which may lead to the ICER/QALY being considered unreliable. In particular, the PBAC considered that there was an overestimation of the clinical benefit and the modelled time horizon. The PBAC noted the sponsor's argument in its Pre-PBAC response that a time horizon of between 10 and 15 years, which has been previously accepted for the treatment of CLL, may not apply to ibrutinib as it has improved survival compared to existing therapy. The PBAC considered that the time horizon would depend on the prognosis of the eligible patient group(s). The PBAC noted the sponsor's argument that a three-state economic model structure, excluding states for progressed disease, reflected the use of ibrutinib in a salvage setting. The PBAC considered that the simplified model structure was inconsistent with the sponsor's proposed 20 year time horizon and the exclusion of further states for disease progression with and without treatment would not capture the additional benefits and costs which would occur over this time period. The PBAC considered that the economic model in any future submission should address the concerns of the ESC and that the model's structure and time horizon should reflect the place in therapy, such as an earlier place in the treatment algorithm may be modelled with additional health states and a longer time horizon than in a salvage setting.
- 7.13 The PBAC considered that the base case ICER of \$45,000 - \$75,000 per QALY at the price proposed was unacceptably high. The PBAC noted that the incremental

cost could be underestimated through using a trial-based assumption for the treatment time with ibrutinib (■■■■ months) which could be longer in practice.

- 7.14 The Pre-PBAC considered that there was insufficient detail to verify the re-specified ICER of \$45,000 - \$75,000 per QALY presented in the Pre-PBAC response which was based on an overall survival estimate which had been adjusted for patient cross over using RPSFTM.
- 7.15 The PBAC noted the issues with the estimated usage and financial implications and advice from DUSC. In particular, the PBAC agreed with its DUSC that the number of patients was underestimated in the submission and there was the potential for use outside the proposed restriction in patients suitable for purine analogues and as a first-line therapy. The PBAC considered that the financial estimates would need to be amended in line with a revised restriction.
- 7.16 The PBAC considered that the following would need to be addressed in a major resubmission: present a revised restriction targeting CLL and SLL patients with relapsed or refractory disease with the highest clinical need; use against the appropriate comparator(s); present evidence to demonstrate the comparative efficacy and safety; and an updated economic evaluation and revised financial estimates. The PBAC considered that an ICER should be between \$50,000 and \$60,000/QALY in order for ibrutinib to be acceptably cost-effective.
- 7.17 The PBAC noted the unmet clinical need for treatments for patients with mantle cell lymphoma and the ongoing trial of ibrutinib in this patient population. In line with the TGA indication, the PBAC would welcome a submission seeking subsidisation of the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.
- 7.18 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

Although disappointed that the PBAC were unable to recommend ibrutinib in the requested setting, Janssen are committed to working with the Department and PBAC in order to ensure timely access to ibrutinib. Janssen believe there is an unmet clinical need for an effective and well tolerated treatment for relapsed or refractory CLL and SLL patients who are unsuitable for treatment or retreatment with a purine analogue