

5.06 IBRUTINIB
Oral capsule, 140 mg,
Imbruvica® ,
Janssen-Cilag Pty Ltd.

1 Purpose of Application

1.1 To request a General Schedule, Authority Required listing for ibrutinib for the treatment of relapsed or refractory mantle cell lymphoma.

2 Requested listing

2.1 The proposed PBS listing is presented below. Suggestions and additions proposed by the PBAC to the requested listing were added in italics with deletions marked in strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
IBRUTINIB ibrutinib 140 mg capsule, 120	1	5	Effective \$ [REDACTED] Published \$ [REDACTED]	IMBRUVICA®	Janssen-Cilag Pty Ltd

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
Episodicity:	<i>Previously treated</i>
Severity:	
Condition:	Mantle cell lymphoma
PBS Indication:	Mantle cell lymphoma
Treatment phase:	<i>Initial treatment</i>
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined

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Clinical criteria:	<p>The condition must have relapsed or be refractory to at least one prior therapy Patient must have received at least one prior therapy for this indication</p> <p>AND</p> <p>Patient must have a WHO performance status score of 2 or less</p> <p>AND</p> <p><i>The treatment must be the sole PBS-subsidised therapy for this condition</i> The treatment must be as monotherapy</p>
Prescriber instructions:	Treatment must be discontinued in patients who experience disease progression while on treatment
Administrative Advice	<i>Special Pricing Arrangements apply.</i>

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Episodicity:	Previously treated
Severity:	
Condition:	Mantle cell lymphoma
PBS Indication:	Mantle cell lymphoma
Treatment phase:	<i>Continuing treatment</i>
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	<p><i>The treatment must be the sole PBS-subsidised therapy for this condition</i></p> <p>AND</p> <p><i>Patient must have previously been issued with an authority prescription for this drug for this condition</i></p> <p>AND</p> <p><i>Patient must have stable or responding disease</i></p>
Administrative Advice	<i>Special Pricing Arrangements apply.</i>

- 2.2 The DUSC noted that the registered indication and requested restriction for ibrutinib do not specify that patients must be relapsed or refractory to prior therapy, only that they have received at least one prior therapy, and therefore that some patients may receive prior therapy for a shorter time period than is clinically appropriate in order to access ibrutinib.
- 2.3 The DUSC also noted that there is the potential for use beyond disease progression as the restriction does not include specific criteria to define progressive disease.
- 2.4 The PBAC agreed with the DUSC and recommended the inclusion of statements to the restriction to limit initial access to patients whose disease has relapsed or is refractory to prior therapy, and to limit continuing access to patients with stable or responding disease.
- 2.5 The submission presented a cost-utility analysis of ibrutinib compared with the nominated comparator, the immunochemotherapy regimen of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP).

3 Background

- 3.1 Ibrutinib was approved by the TGA on 27 April 2015 for the treatment of:
- Patients with mantle cell lymphoma who have received at least one prior therapy; and
 - Patients with chronic lymphocytic leukaemia/small lymphocytic lymphoma who have received at least one prior therapy or as first line in patients with chronic lymphocytic leukaemia with 17p deletion.
- 3.2 This was the first submission to the PBAC for the listing of ibrutinib for mantle cell lymphoma.
- 3.3 Ibrutinib has been considered by the PBAC four times previously for the treatment of relapsed or refractory chronic lymphocytic leukaemia and/or small lymphocytic lymphoma (July 2015: major submission; November 2015, March 2016 and July/August 2016: minor re-submissions). The PBAC rejected the August 2016 submission.
- 3.4 The proposed effective price per capsule for ibrutinib for the treatment of mantle cell lymphoma is [REDACTED]. The ESC noted that the recommended ibrutinib dose is 560 mg per day for mantle cell lymphoma and 420 mg per day for chronic lymphocytic lymphoma resulting in a higher effective price for the mantle cell lymphoma indication.
- 3.5 Lenalidomide, which is TGA registered for use in relapsed or refractory mantle cell lymphoma, was rejected by the PBAC for this indication at the July 2016 meeting, on the basis of uncertain effectiveness, and uncertain cost-effectiveness.

4 Clinical place for the proposed therapy

- 4.1 Mantle cell lymphoma is a rare and aggressive subtype of non-Hodgkin lymphoma. It is characterised by the overexpression of cyclin D1, leading to cell cycle deregulation and proliferation of B-cells in the mantle zone of lymph nodes.
- 4.2 Ibrutinib was proposed for patients with relapsed or refractory mantle cell lymphoma who have received at least one prior therapy. Ibrutinib is to be given as monotherapy until disease progression or toxicity.

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

5 Comparator

- 5.1 The nominated comparator was immunochemotherapy, specifically R-CHOP, as the submission considered that R-CHOP was the most commonly used immunochemotherapy regimen used in Australian clinical practice and was representative of the efficacy and safety of immunochemotherapy in relapsed or refractory mantle cell lymphoma patients. This might be an appropriate comparator, although other rituximab-based regimens could also be considered appropriate comparators. The ESC noted that, especially in young, fit patients, R-CHOP is a common first line therapy, and hence is not an appropriate comparator for relapsed or refractory mantle cell lymphoma. It was argued in the Pre-Subcommittee Response (PSCR) (p2) that in Australian clinical practice bendamustine with rituximab (BR) is used as a first line treatment and upon disease progression R-CHOP is used. The ESC considered BR is generally only used in the more elderly less fit patients, and that there is no standard therapy for patients with relapsed or refractory disease. It was further noted that a more aggressive regimen (e.g. rituximab together with combination chemotherapy including an alkylator or platinum agent) is commonly used in relapsed or refractory disease. The PBAC agreed with the Pre-PBAC response that BR is commonly used as a first line therapy in mantle cell lymphoma, and considered R-CHOP an appropriate comparator in relapsed or refractory mantle cell lymphoma, although noted other immunochemotherapy regimens may also be used.
- 5.2 For the assessment of efficacy, the clinical comparator was temsirolimus, which the submission claimed represented R-CHOP. The appropriateness of this assumption is discussed with the evidence below.
- 5.3 For the assessment of safety, the submission considered the use of R-CHOP in patients with newly diagnosed mantle cell lymphoma represented R-CHOP in patients with relapsed or refractory disease. The appropriateness of this assumption is discussed with the evidence below.

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 (21), health care professionals (2) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with ibrutinib including fewer side effects, possible avoidance of stem cell therapy, ease of administration and the ability to resume a normal life with a better quality of life than standard treatment with chemotherapy.

Clinical trials

6.3 The submission was based on one head-to-head trial, MCL-3001, comparing ibrutinib to temsirolimus (N = 280). Two additional randomised trials were used in a naïve comparison of efficacy and three additional trials were used to compare safety.

6.4 The submission firstly compared ibrutinib to temsirolimus using the results from the randomised controlled trial, MCL-3001. Then,:

- to inform the comparative efficacy of ibrutinib with R-CHOP, a naïve comparison was performed between the temsirolimus arm of MCL-3001 and subgroups of mantle cell lymphoma patients who received -
 - rituximab plus fludarabine (FR) (Rummel 2016); and
 - rituximab, fludarabine, cyclophosphamide and mitozantrone (R-FCM) (Forstpointner 2004).
- to inform the comparative safety of ibrutinib with R-CHOP, a naïve comparison was performed between the ibrutinib arm of MCL-3001 and:
 - R-CHOP in treatment naïve patients with mantle cell lymphoma (Lenz 2005, Kluin-Nelemans 2012 and Robak 2015).

6.5 The ESC and the PBAC noted that no direct head to head randomised trials were available and that efficacy and safety were compared using naïve indirect comparisons. The PBAC noted the statement in the Pre-PBAC response (p1) that there are no trials comparing ibrutinib with immunochemotherapy in the treatment of mantle cell lymphoma, and it is unlikely that there will be any randomised trials conducted in the future with R-CHOP or other immunochemotherapy regimens because internationally, targeted therapies are considered the standard of care for mantle cell lymphoma.

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

Table 1: Randomised controlled trials presented in the submission

Trial ID	Protocol title/Publication title	Publication citation
Direct randomised trials – ibrutinib versus temsirolimus		
MCL-3001	A randomised, controlled, open-label, multicentre, Phase 3 study of the Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib, versus temsirolimus in subjects with relapsed or refractory mantle cell lymphoma who have received at least one prior therapy. Dreyling M, Junczak W, Jerkeman M, <i>et al.</i> Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, Phase 3 study.	11 September 2015 <i>The Lancet.</i> 2016; 307: 770-778.
Supplementary randomised trials – proxy for efficacy of R-CHOP		
Forstpointner (2004)	Forstpointner R, Dreyling M, Repp R, <i>et al.</i> The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomised study of the German Low Grade Lymphoma Study Group.	<i>Blood.</i> 2004; 104(10): 3064-3071.
Rummel (2016)	Rummel M, Kaiser U, Basler C, <i>et al.</i> Bendamustine plus rituximab versus fludarabine plus rituximab for patients with relapsed indolent and mantle cell lymphomas: a multicentre, randomised, open-label, non-inferiority Phase 3 trial.	<i>Lancet Oncology.</i> 2016; 17: 57-66.
Supplementary randomised trials – safety of R-CHOP		
Lenz (2005)	Lenz G, Dreyling M, Hoster E, <i>et al.</i> Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated Mantle Cell Lymphoma: Results of a prospective randomised trial of the German Low Grade Lymphoma Study Group (GLSG).	<i>Journal of Clinical Oncology.</i> 2005; 23(9): 1984-1992.
Kluin-Nelemans (2012)	Kluin-Nelemans H, Hoster E, Hermine O, <i>et al.</i> Treatment of older patients with mantle-cell lymphoma.	<i>New England Journal of Medicine.</i> 2012; 367: 520-531.
Robak (2015)	Robak T, Huang H, Jie J, <i>et al.</i> Bortezomib-based therapy for newly diagnosed Mantle-cell lymphoma.	<i>New England Journal of Medicine.</i> 2015; 372: 944-953.

Source: Table B.11, pp12-13, Section B of the submission

R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

6.7 The key features of the randomised trials are summarised in the table below.

Table 2: Key features of trials used in the efficacy and safety comparisons

Trial	N	Design/ median follow-up	Risk of bias	Patient population	Outcomes	Used in modelled evaluation
Ibrutinib versus temsirolimus						
MCL-3001	280	R, OL, MC 20.0 months	Unclear	Relapsed or refractory MCL	PFS, OS, Safety	Yes
Efficacy – proxy for R-CHOP						
Forstpointner (2004)	24 ^a	R*, OL, MC 18 months	Unclear	Relapsed or refractory MCL	ORR, PFS, OS, Safety	No
Rummel (2016)	47 ^b	R*, OL, MC 96 months	High	Relapsed or refractory MCL	PFS, OS, ORR, Safety	No
Safety – R-CHOP						
Lenz (2005)	62 ^c	R*, OL, MC 18 months	Unclear	Untreated FL, MCL or LL; Stage III-IV	ORR, TTF, Safety	Yes
Kluin-Nelemans (2012)	239 ^e	R*, OL, MC 37 months	High	Newly diagnosed MCL; ≥ 60 years;	ORR, TTF, Safety	Yes
Robak (2015)	244 ^f	R*, OL, MC 40 months	Unclear	Newly diagnosed MCL; Stage II-IV	PFS, ORR, Safety	Yes

Source: compiled during the evaluation

FL = follicular lymphoma; LL = lymphoplasmacytic lymphoma; MC = multi-centre; MCL = mantle cell lymphoma; OL = open label; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; R = randomised; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; TTF = time to treatment failure

* Although the trials used to support efficacy and safety were randomised, data for efficacy was taken from the subgroup of patients with MCL, and for safety, from the R-CHOP arm only

^a N = 128 evaluable patients; 48 of whom had MCL. Of the 48 who had MCL, 24 received rituximab, fludarabine, cyclophosphamide, mitozantrone and were considered in the naïve efficacy comparison.

^b N = 219 patients; 47 of whom had MCL and were considered in the naïve efficacy comparison

^c N = 122; 62 of whom were treated with R-CHOP and were considered in the evaluation of safety

^d N = 485; 239 of whom were treated with R-CHOP and were considered in the evaluation of safety

^e N = 487; 244 of whom were treated with R-CHOP and were considered in the evaluation of safety

6.8 Patients treated in the MCL-3001 trial were allowed to crossover after the independent review committee confirmed progression. A total of 32 patients (22.7%) initially randomised to temsirolimus were exposed to ibrutinib.

6.9 The ESC noted that temsirolimus was selected as the comparator in Study MCL-3001 on the basis of previously being demonstrated in a randomised trial to increase progression free survival versus investigator's choice single agent therapy. However, the ESC considered that temsirolimus may not be the most effective treatment used in relapsed or refractory mantle cell lymphoma. The ESC noted the arguments in the PSCR (p2) that, based on a naïve comparison, PFS with temsirolimus was similar to that with FR although also noted that FR (and R-FCM) is not routinely used in relapsed or refractory mantle cell lymphoma. The PSCR (p2) further argued that the efficacy of R-CHOP is unlikely to be significantly different to FR and R-FCM as these regimens share rituximab and cyclophosphamide as common treatments.

Comparative effectiveness

6.10 The results from MCL-3001 are summarised in the table below.

Table 3: Results of progression free survival and overall survival from trial MCL-3001 (ITT population)

	Ibrutinib (n = 139)	Temsirolimus (n = 141)	Hazard ratio (95% CI) ^a	
Progression free survival (IRC assessed)				
Median follow-up, months	20.3	19.7		
Patient status, n (%):				
Progressed or died	73 (53%)	111 (79%)		
Censored	66 (48%)	30 (21%)		
Median PFS, months (95% CI) ^b :	14.6 (10.4, NE)	6.2 (4.2, 7.9)	0.43 (0.32, 0.58)	
Overall survival				
Median follow-up, months (95% CI)	20.0 (19.4, 20.6)			
Patient status, n (%):				
Progressed or died	59 (42%)	63 (45%)		
Censored	80 (58%)	78 (55%)		
Crossover/ subsequent ibrutinib	0	32 (23%)		
OS, months (95% CI) ^b :			ITT	0.76 (0.53, 1.09)
25% quartile	██████████	██████████	RPSFT model	██████████
Median	NE (18.6, NE)	21.3 (13.0, NE)	IPE algorithm	██████████
			IPCW method	██████████

Source: Tables B.29 and B.30, pp43-44, and Table B.31, p47, Section B of the submission and Table C.14, p49, Section C of the submission

CI = confidence interval; IPCW = inverse probability of censoring weight; IPE = iterative parameter estimation; IRC = independent review committee; ITT = intent-to-treat; NE = not estimable; OS = overall survival; PFS = progression free survival; RPSFT = rank preserving structural failure time; **Bold** = statistically significant

^a Based on stratified Cox's model

^b Based on Kaplan-Meier product limit estimates

- 6.11 At the time of the clinical cut-off, the median follow-up was 20.3 months in the ibrutinib arm and 19.7 months in the temsirolimus arm, and 73 patients (53%) in the ibrutinib arm and 111 (79%) in the temsirolimus arm had progressed or died. The median progression free survival was 14.6 months for ibrutinib and 6.2 months for temsirolimus (hazard ratio (HR) = 0.43; 95% confidence interval (CI): 0.32 to 0.58).
- 6.12 At the time of the clinical cut-off, 59 (42%) and 63 (45%) patients had died in the ibrutinib and temsirolimus arms respectively. The median overall survival was not reached in the ibrutinib arm; it was 21.3 months in the temsirolimus arm. The ESC noted that the difference in overall survival was not statistically significant (intention to treat analysis: HR = 0.76; 95% CI: 0.53 to 1.09); however, the trial was not powered to detect a significant improvement in overall survival.
- 6.13 The submission stated that crossover, which allowed patients in the temsirolimus arm to receive ibrutinib following progression, resulted in overall survival being overestimated for temsirolimus. Therefore, the submission presented analyses adjusting for crossover. The submission stated a preference for the Rank preserving structural failure time (RPSFT) model. This model appeared to be reasonable, as there did appear to be a common treatment effect. That is, the overall survival of patients who were randomised to ibrutinib and those who received ibrutinib after crossover was comparable. Similar results were observed using both an Iterative Parameter Estimation (IPE) and Inverse Probability of Censoring Weights (IPCW) approach.
- 6.14 The hazard ratios for the adjusted overall survival analyses were all similar to that for the intention to treat analysis, and all remained non-significant. In the economic

model, the submission used the RPSFT model time-to-event endpoint data from the adjusted overall survival Kaplan-Meier curve.

- 6.15 The ESC noted the submission appropriately assessed the impact of cross-over on the hazard ratio for overall survival using three adjustment methods. The results indicated that cross-over did not impact on the estimated hazard ratio.
- 6.16 The submission presented a naïve comparison of progression free survival and overall survival for patients treated with temsirolimus in the MCL-3001 trial versus patients treated with other immunochemotherapies. The ESC noted that the trials for the rituximab regimens had very small numbers of patients enrolled. The PSCR (p2) stated the Rummel (2016) trial included patients with a more favourable prognosis than patients in MCL-3001.

Table 4: Efficacy results for temsirolimus from MCL-3001 compared with other immunochemotherapies

	Treatment	Median PFS, months (95% CI)	Median OS, months (95% CI)
MCL-3001	Temsirolimus (n = 141)	6.2 (4.2, 7.9)	21.3 (13.0, NE)
Forstpointner (2004)	R-FCM (n = 24)	8 (NR)	NE; 65% alive at 2 years
Rummel (2016)	R-F (n = 23)	4.7 (2.3, 11.2)	20.9 (10.6, 56.7)
	R-B (n = 24)	17.6 (7.9, 30.4)	35.3 (14.9, NE)

Source: Table C.4, p13, Section C of the submission

CI = confidence interval; NE = not estimable; NR = not reported; OS = overall survival; PFS = progression-free survival; R-B = rituximab, bendamustine; R-F = rituximab, fludarabine; R-FCM = rituximab, fludarabine, cyclophosphamide, mitozantrone

- 6.17 The median progression free survival for patients treated with R-FCM in Forstpointner (2004) (8 months) was similar to that for patients treated with temsirolimus in MCL-3001 (6.2 months). The median progression free and overall survival for patients treated with FR in Rummel (2016) (4.7 and 20.9 months) was similar to that for patients treated with temsirolimus in MCL-3001 (6.2 and 21.3 months).
- 6.18 The submission stated that the results of this comparison demonstrated that temsirolimus was comparable to R-CHOP in terms of efficacy. The ESC considered that this was not supported by the data in the submission.
- 6.19 Based on the naïve indirect comparison, the median progression free and overall survival for patients treated with BR were longer than for patients treated with FR, temsirolimus or R-FCM. The Pre-PBAC response (p2) stated a comparison of BR and temsirolimus is inappropriate because BR is increasingly being used in the first line setting and bendamustine is not PBS listed for use in the relapsed/refractory setting. The ESC noted the median progression free survival varied across the regimens.

Comparative harms

- 6.20 The adverse events reported with ibrutinib in relapsed/refractory mantle cell lymphoma patients (from MCL-3001) and with R-CHOP in treatment naïve mantle cell lymphoma patients (from Robak 2015) are summarised below.

Table 5: Adverse event profile for ibrutinib and tamsirolimus from trial MCL-3001 (SAS) and R-CHOP from Robak (2015)

	MCL-3001		Robak (2015)
	Ibrutinib (n = 139)	Tamsirolimus (n = 139)	R-CHOP (n = 242)
Median treatment duration	14.4 months	3.0 months	3.7 months
Any TE AE	138 (99%)	138 (99%)	238 (98%)
≥ Grade 3			206 (85%)
Drug related			226 (93%)
Any TE SAE			72 (30%)
≥ Grade 3			-
Drug related			50 (21%)
AE resulting in discontinuation			17 (7%)
AE resulting in death			12 (5%)

Source: Table B.38, p60, Section B of the submission

AE = adverse event; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; SAE = serious adverse event; SAS = safety analysis set; TE = treatment-emergent

- 6.21 The ESC considered that safety data for ibrutinib in chronic lymphocytic leukaemia patients was relevant for the current submission and noted a recent update presented at the American Society of Hematology (ASH) meeting in which data from 4 studies with 1,505 patients were pooled. Of these patients, 756 received ibrutinib alone or with BR and 749 received a comparator treatment. In the ibrutinib treated patients, 49 (6.5%) developed treatment-related atrial fibrillation compared with 12 (1.6%) patients receiving comparator treatments. The ESC noted the potential for ibrutinib to cause atrial fibrillation was not discussed in the submission, and the costs associated with monitoring for atrial fibrillation were not included in the economic model or financial forecasts.
- 6.22 The PBAC noted the comments in the Pre-PBAC response (p3) that based on the most recent Periodic Safety Update Report (PSUR) for ibrutinib the majority of atrial fibrillation events occurred in chronic lymphocytic leukaemia patients (138 events), not mantle cell lymphoma patients (40 events), with predisposing confounding factors such as concomitant use of anticoagulants and comorbidities. The PBAC considered that the potential increased risk of atrial fibrillation associated with ibrutinib treatment remained a concern for mantle cell lymphoma. The PBAC further noted that mantle cell lymphoma is more common in the elderly and these patients may be predisposed to atrial fibrillation and the implications of atrial fibrillation may be more significant.

Benefits/harms

- 6.23 A summary of the benefits and harms for ibrutinib and tamsirolimus/immunochemotherapy/R-CHOP is presented in the table below.

Table 6: Naïve comparisons between ibrutinib and immunochemotherapy/R-CHOP

EFFICACY								
	ibrutinib	Temsirolimus	Immunochemotherapy	Absolute Difference	HR (95% CI)			
Progression free survival – median (months)								
MCL-3001	14.6 (10.4, NE)	6.2 (4.2, 7.9)	-	8.4	0.43 (0.32, 0.58)			
Rummel (2016)	-	-	R-F = 4.7 (2.3, 11.2)	NC	NC			
			R-B = 17.6 (7.9, 30.4)	NC	NC			
Forstpointner (2004)	-	-	R-FCM = 9 (NR)	NC	NC			
Overall survival – median (months)								
MCL-3001	NE (18.6, NE)	21.3 (13.0, NE)	-	NE	0.76 (0.53, 1.09)			
Rummel (2016)	-	-	R-F = 20.9 (10.6, 56.7)	NC	NC			
			R-B = 35.3 (14.9, NE)	NC	NC			
Forstpointner (2004)	-	-	R-FCM = NE	NC	NC			
HARMS								
	ibrutinib	TEM	R-CHOP	RR (95% CI)	Event rate/100 patients*			RD (95% CI)
					ibrutinib	TEM	R-CHOP	
Neutropenia (≥ Grade 3)								
MCL-3001	18/139	23/139		0.78 (0.44, 1.38)	12.9	16.5		-0.04 (-0.12, 0.5)
Robak (2015)	-	-	162/242	NC	-	-	66.9	NC
Kluin-Nelemans (2012)	-	-	149/249	NC	-	-	60	NC
Fatigue (≥ Grade 3)								
MCL-3001	6/139	10/139	-	0.60 (0.22, 1.61)	4.3	7.2		-0.03 (-0.08, 0.03)
Kluin-Nelemans (2012)	-	-	15/249	-	-	-	6	NC
Diarrhoea (any Grade)								
MCL-3001	40/139	43/139	-	0.93 (0.65, 1.33)	28.8	30.9		-0.02 (-0.13, 0.09)
Robak (2015)	-	-	22/242	NC	-	-	9.1	NC

Source: Tables B.29 and B.30, pp43-44, Table B.31, p47, and Tables B.40 and B.41, pp63-64, Section B of the submission; and Table C.4, p13, and Table C.9, p29, Section C of the submission

CI = confidence interval; HR = hazard ratio; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; NC = not calculable; NE = not estimable; R-B = rituximab, bendamustine; RD = risk difference; R-F = rituximab, fludarabine; R-FCM = rituximab, fludarabine, cyclophosphamide, mitozantrone; RR = relative risk; TEM = temsirolimus; **Bold** = statistically significant

* Median duration of treatment MCL-3001, ibrutinib arm = 14.4 months, TEM arm = 3.0 months; Robak = 3.7 months; Kluin-Nelemans = 5.0 months

- 6.24 The submission did not present any evidence of the efficacy of R-CHOP in patients with relapsed/refractory mantle cell lymphoma. On the basis of the naïve comparison of ibrutinib with FR and R-FCM, which acted as proxies for R-CHOP, the ESC noted that it was not possible to assess the relative efficacy of ibrutinib and R-CHOP.
- 6.25 The submission did not present any evidence of the safety of R-CHOP in patients with relapsed/refractory mantle cell lymphoma. On the basis of the naïve comparison of ibrutinib with R-CHOP as a first-line treatment, the ESC noted that it was not possible to assess the relative safety of ibrutinib and R-CHOP in relapsed/refractory disease.

Clinical claim

Ibrutinib versus temsirolimus

- 6.26 The submission described ibrutinib as superior in terms of comparative effectiveness and superior in terms of comparative safety over temsirolimus for the treatment of patients with relapsed or refractory mantle cell lymphoma.
- 6.27 The ESC advised that the claim of superior effectiveness might not be adequately supported as:
- randomisation in the clinical trial might not have been completely successful as fewer patients in the ibrutinib arm (26%) had refractory disease compared with in the temsirolimus arm (33%);
 - although ibrutinib showed superior progression free survival, no statistically significant improvement in overall survival was observed (without or with adjustment for crossover); and
 - the open-label nature of the trial might have resulted in a larger proportion of patients treated with temsirolimus discontinuing treatment due to adverse events, investigator or funder decisions or refusal of further treatment.
- 6.28 The claim of superior safety was adequately supported for short-term treatment, with ibrutinib resulting in a lower incidence of adverse events when compared with temsirolimus. The long-term safety profile of ibrutinib remains unknown. .

Ibrutinib versus R-CHOP

- 6.29 The submission described ibrutinib as superior in terms of comparative effectiveness and superior in terms of comparative safety over R-CHOP for the treatment of patients with relapsed or refractory mantle cell lymphoma.
- 6.30 The ESC considered that the submission's claim that ibrutinib was superior in terms of effectiveness compared with R-CHOP was not supported as a clinical trial comparing ibrutinib with temsirolimus was presented and the temsirolimus was compared with immunochemotherapies (FR and R-FCM) which were used as a proxy for R-CHOP. The issues with this approach were:
- the comparison between temsirolimus and the immunochemotherapies was naïve as there was no common comparator;
 - no evidence was provided to support the assumption that R-CHOP was comparable to FR or R-FCM in terms of efficacy;
 - patient numbers in the immunochemotherapy trials were very small (< 25) making comparisons uncertain;
 - Rummel (2016) and Forstpointner (2004) results were based on subgroup analyses, which might have introduced bias; and
 - if BR was considered a relevant immunochemotherapy, the efficacy of temsirolimus would not be an adequate proxy for immunochemotherapy, as BR was superior to FR in patients with relapsed mantle cell lymphoma, albeit subject to analysis of very small patient numbers (Rummel 2016).
- 6.31 The ESC considered that the submission's claim that ibrutinib was superior in terms of safety compared with R-CHOP was not supported as a clinical trial comparing

ibrutinib with temsirolimus was presented and the safety of ibrutinib was compared with R-CHOP in the treatment of newly diagnosed mantle cell lymphoma. The issues with this approach were:

- the comparison between ibrutinib and R-CHOP was naïve as there was no common comparator; and
- the patient groups were not comparable – ibrutinib was given to patients with relapsed or refractory mantle cell lymphoma, whereas the R-CHOP trials were in patients with newly diagnosed mantle cell lymphoma. The PSCR (p3) argued that this biased the comparison against ibrutinib as patients in the R-CHOP studies were younger, not previously treated, had more bone marrow reserve and may have less co-morbidities.

6.32 The PBAC considered that the claim of superior comparative effectiveness over R-CHOP was reasonable based on the endpoint of progression free survival, however considered the magnitude of the benefit to be uncertain because the comparison utilised a naïve indirect comparison. The PBAC considered the uncertainty associated with the magnitude of the gain in overall survival was even greater because a statistically significant gain has not been demonstrated.

6.33 The PBAC considered that the claim of superior comparative safety over R-CHOP was not adequately supported by the data. The PBAC noted that ibrutinib appears to be associated with a reduced risk of neutropenia, however noted the emerging data suggesting ibrutinib may be associated with an increased risk of atrial fibrillation.

Economic analysis

6.34 The submission presented a partitioned survival economic evaluation, based on a randomised trial (MCL-3001) that compared ibrutinib with temsirolimus and naïve comparisons between temsirolimus and other rituximab-based regimens as a proxy for the main comparator R-CHOP.

Table 7: Summary of model structure and rationale

Time horizon	Lifetime (15 year) time horizon in the model base case versus 28 months in MCL-3001
Outcomes	LYs and QALYs
Method used to generate results	Cohort analysis
Cycle length	30 days (1 month) with half-cycle correction
Transition probabilities	PFS: KM curve up to 19 months for ibrutinib and 12 months for temsirolimus – extrapolation using exponential model. OS: KM curve up to when 20% of randomised patients remained in risk set (RPSFT model adjusted) – extrapolation using exponential model.
Discount rate	5% for costs and outcomes
Software package	Excel 2010

Source: Section D.3, pp6-9, Section D of the submission

KM = Kaplan-Meier; LY = life year; OS = overall survival; PFS = progression free survival; QALY = quality-adjusted life year; RPSFT = rank preserving structural failure time

6.35 The ESC advised that the use of a 15 year time horizon was overly optimistic given that the overall survival following relapse or upon becoming refractory is approximately two years. The ESC noted that the specific issue was not the time horizon but the extrapolations which resulted in a substantial proportion of patients being progression free at 5 years (██████ of ibrutinib treated patients vs ██████ of R-

CHOP patients) and alive at 5 years (██████████) and 10 years (██████████). The sensitivity analyses presented in the submission and PSCR assessing the impact of shorter time horizons did not address the extrapolation issues as the curves did not converge within the stated time horizon.

6.36 The key drivers of the economic model are provided below.

Table 8: Key drivers of the model

Description	Method/Value	Impact
PFS gains	Efficacy of R-CHOP was assumed to be the same as the efficacy of temsirolimus in MCL-3001 Non-blinded trial (potential for differential diagnosis of progression) Extrapolation not conservative	High; likely to favour ibrutinib
OS gains	The OS difference in the clinical trial was not statistically significant; however, the model included OS gains for ibrutinib Extrapolation not conservative	High, favours ibrutinib
Adjustment for crossover	RPSFT method was used to adjust OS for crossover in the temsirolimus/R-CHOP arm	Moderate; favours ibrutinib
Disutilities due to adverse events	Adverse events were specifically considered for R-CHOP patients only. Relatively high utility decrements were applied to the represented adverse events	High; favours ibrutinib

Source: compiled during the evaluation

OS = overall survival; PFS = progression free survival; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RPSFT = rank preserving structural failure time

6.37 A summary of the disutilities for adverse events applied to R-CHOP patients only is presented in Table 9. The PSCR (p4) stated that the disutilities from Nafees (2016) are appropriate as they are obtained from a sample of the Australian general population and therefore are applicable to the Australian setting. The ESC noted that the disutilities applied were substantially larger than reported in other studies presented in the submission i.e. a disutility of 0.49 for febrile neutropenia based on Nafees (2016) vs 0.09-0.15 in other studies; 0.50 for neutropenia vs 0.08-0.16; 0.49 for fatigue vs 0.07-0.12 and 0.17 for hair loss vs 0.03-0.11.

Table 9: Summary of the disutilities due to adverse events applied to R-CHOP patients

	Disutility	When the disutility was applied	% patients experiencing AE
≥ Grade 3 neutropenia	0.50	Cycle 1; Duration = 1 cycle.	63.3%
≥ Grade 3 febrile neutropenia	0.49		15.3%
≥ Grade 3 alopecia	0.17	Cycles 1-8; Duration of treatment	67.0%
Any Grade fatigue	0.49		38.9%
Any Grade peripheral neuropathy	0.14		34.4%

Source: Table C.29, p91, Section C of the submission

AE = adverse event; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

6.38 The submission applied the disutilities associated with neutropenia and febrile neutropenia in Cycle 1 only. For alopecia, fatigue and peripheral neuropathy, the disutilities were applied for the duration of treatment (i.e. for up to eight cycles of R-CHOP). This might not have been appropriate.

6.39 The ESC noted that the same baseline utility was applied in the first cycle for both treatment arms, however in subsequent cycles a lower baseline utility was applied to the R-CHOP arm (0.733) compared with the ibrutinib arm (0.79). The ESC

considered the baseline utility should be the same for both treatments. The PSCR (p4) stated that the utility values for ibrutinib were sourced directly from patients whilst on ibrutinib treatment and hence directly captured disutilities associated with AEs (which justified including disutilities for adverse events in the R-CHOP arm only). The ESC considered that this would suggest that the baseline utility for ibrutinib should be lower than for R-CHOP.

- 6.40 Table 10 shows the proportions of patients experiencing the specific adverse events and the assumed utility decrements for patients in the R-CHOP arm of the model. The utility decrements were applied additively. The resulting utility values applied in the first and second cycles of the model are [REDACTED] and [REDACTED] respectively for ibrutinib and [REDACTED] and [REDACTED] for R-CHOP. These differences were considered implausible by the ESC.

Table 10: Summary of the proportions of patients experiencing alternative AEs and the associated utility decrements

	ibrutinib	R-CHOP	Disutility
Neutropenia	0.13	0.63	0.5
Febrile neutropenia	0.02	0.15	0.49
Alopecia	0.00	0.67	0.17
Peripheral neuropathy	0.03	0.34	0.14
Fatigue	0.22	0.39	0.49

Compiled by ESC during evaluation.

- 6.41 The results of the stepped economic evaluation are presented below.

Table 11: Results of the stepped economic evaluation

Step and component	ibrutinib	R-CHOP	Increment
Step 1: Trial-based costs and LYs over 28 month trial time horizon			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/LY			\$ [REDACTED]
Step 2: Trial results and QALYs over 28 month trial time horizon			
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/QALY			\$ [REDACTED]
Step 3: Modelled evaluation over lifetime (15 year) time horizon			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYs	[REDACTED]	[REDACTED]	[REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/LY			\$ [REDACTED]
Incremental cost/QALY			\$ [REDACTED]

Source: Tables D.4-D.6, pp13-15, Section D of the submission

LY = life year; QALY = quality-adjusted life year; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

- 6.42 The submission presented a base case incremental cost per LYG of \$105,000 - \$200,000 and an incremental cost of \$75,000 - \$105,000 per QALY gained.
- 6.43 Step 1 of the economic evaluation resulted in 0.17 life years gained. Step 2 of the economic evaluation, converted life years gained to QALYs gained and resulted in an incremental gain of 0.43 QALYs over the 28 month trial time horizon. This large difference was due to the incorporation of relatively large disutilities for adverse

events for patients treated with R-CHOP only and the higher baseline utility for patients in the ibrutinib arm compared with the R-CHOP arm.

- 6.44 The ICER was uncertain due to:
- the use of the MCL-3001 trial to estimate clinical efficacy of R-CHOP, as the evidence provided in the submission did not support the claim that temsirolimus was equivalent to R-CHOP in terms of efficacy;
 - the short trial duration (28 months) compared with the model duration (15 year lifetime). The use of a 15 year time horizon might not have been appropriate as prognosis following relapse or becoming refractory is poor, with an average overall survival of approximately two years;
 - the cost of subsequent therapy in the post-progression health state being lower for ibrutinib (\$██████████) compared with R-CHOP (\$██████████);
 - the magnitude of the disutilities applied to adverse events and the fact that disutilities were applied to R-CHOP patients only; and
 - although no statistically significant improvement in overall survival was demonstrated in the clinical trial, the submission applied an exponential extrapolation of overall survival in the model beyond the trial duration resulting in a survival gain for ibrutinib. The exponential distribution did not fit the data best by Akaike information criterion and Bayesian information criterion statistics. The submission excluded the log-logistic, log-normal and gamma distributions from its consideration as they would not reflect long-term overall survival.
- 6.45 The ESC noted that the increase in overall survival with ibrutinib in MCL-3001 was not statistically significant and if a survival benefit was to be modelled it may have been more appropriate to select a conservative pair of parametric curves rather than exponential for both arms.
- 6.46 The results for the key sensitivity analyses are presented below.

Table 12: Selected results from the sensitivity analyses

	Δ costs	Δ QALYs	ICER
Base case	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Time horizon (base case = lifetime/15 year):			
10 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
7 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
5 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
OS estimates (base case = crossover adjusted using RPSFT model):			
ITT	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Censored at second protocol amendment – removal of crossover	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
IPE algorithm	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
IPCW adjusted	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
ITT OS rate from ibrutinib arm used for R-CHOP arm	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Maximum number of cycles of R-CHOP patients receive (base case = 8):			
6	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
4	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Cost of subsequent therapy for ibrutinib patients (base case = \$1,892.76):			
As per R-CHOP patients = \$2,780.65	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
AE disutilities:			
Neutropenia = 0.23 (base case = 0.50)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Alopecia = 0.09 (base case = 0.17)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Alopecia = 0 (base case = 0.17)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Fatigue = 0.20 (base case = -0.49)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
All AE sensitivity disutilities	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
All AE disutilities = 0	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]

Source: Table D.7, p18, Section D of the submission

AE = adverse event; ICER = incremental cost-effectiveness ratio; IPCW = inverse probability of censoring weights; IPE = iterative parameter estimation; ITT = intent-to-treat; OS = overall survival; QALY = quality-adjusted life year; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RPSFT = rank preserving structural failure time

- 6.47 The economic model was sensitive to reducing the time horizon, the overall survival estimates and the disutilities assigned to adverse events experienced by patients in the R-CHOP arm. Applying the same rate of overall survival to both arms of the model increased the ICER to \$105,000 - \$200,000. Using the adverse event disutilities from the literature increased the ICER to \$105,000 - \$200,000. Removing the adverse events disutilities resulted in an ICER of \$105,000 - \$200,000. The ESC noted this scenario included additional costs in the R-CHOP arm for the treatment of adverse events.

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

- 6.48 The average cost per cycle/month for ibrutinib was \$ [REDACTED], based on the proposed effective dispensed price for maximum quantity (DPMQ) of \$ [REDACTED] and a dose intensity of [REDACTED]% from the key clinical trial. Treatment continues until disease progression or toxicity. In the economic model, the average length of treatment was [REDACTED] months. It was assumed that this period would require [REDACTED] packs (one pack = 30 days of treatment). The total cost per patient per course was estimated to be \$ [REDACTED].
- 6.49 The average cost of R-CHOP was estimated to be \$ [REDACTED] per cycle, based on the DPMQs of each component, a 32% versus 68% split across public and private hospital use and an average patient body surface area of 1.84 kg/m². In the

economic model the average patient received [REDACTED] cycles, which equated to a total drug cost of \$[REDACTED] per patient.

Estimated PBS usage & financial implications

6.50 The submission was considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial implications associated with the requested PBS listing of ibrutinib for relapsed or refractory MCL.

Table 13: Estimated utilisation and cost to the PBS in the first five years of listing based on proposed effective price

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number commencing treatment ¹	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Months of treatment Prescriptions ²	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	\$[REDACTED]	\$[REDACTED]	\$[REDACTED]	\$[REDACTED]	\$[REDACTED]
Net cost to MBS	\$0	\$0	\$0	\$0	\$0
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$[REDACTED]	\$[REDACTED]	\$[REDACTED]	\$[REDACTED]	\$[REDACTED]

Source: Submission and compiled by DUSC

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

¹ The submission did not estimate the total number of patients who will be dispensed a script each year but costs for continuing treatment have been factored into the calculation of the number of packs.

² Assuming 23.4 months of treatment per patient, as estimated by the submission.

6.51 In year 1, the estimated number of patients commencing treatment was less than 10,000 and the net cost to the PBS would be \$20 - \$30 million, increasing to \$30 - \$60 million in year 2. In year 5, the estimated number of patients commencing treatment was less than 10,000 and the net cost to the PBS would be \$20 - \$30 million.

6.52 DUSC considered that the estimates presented in the submission were overestimated. The main issues were:

- The number of incident patients and the starting cohort of prevalent patients were overestimated because of:
 - The implausible assumption that all incident patients not only survived first-line treatment, but were alive two years after diagnosis and had relapsed.
 - The assumption that all 15-year prevalent patients would relapse.
 - Basing the prevalent population on linear extrapolations of Australian Institute of Health and Welfare (AIHW) data which exceed overall population growth.
- The submission’s estimate of the prevalent population ([REDACTED]) was high relative to the number of people who are estimated to be living with MCL in Australia (1,000). As such, DUSC considered the modelling of the treated population lacked face validity. The submission’s estimate of [REDACTED] patients treated with ibrutinib in Year 1 was also considered to be overestimated as the eligibility criteria would further restrict the treated population to those who are relapsed or refractory with a WHO performance status of 2 or less. The starting cohort of

prevalent patients was further overestimated by assuming that all prevalent patients with MCL would relapse and become eligible for treatment.

- There is a potential for ibrutinib to be used in combination with other agents. This would not be in accordance with the requested restriction or the evidence provided in the submission but such use was being trialled in several studies at the time of investigation.

Quality Use of Medicines

- 6.53 The submission stated that the quality use of ibrutinib would be ensured through the provision of education resources and support to patients and clinicians and the development of a dedicated adherence program for patients. The ESC noted that this should include monitoring for atrial fibrillation.

Financial Management – Special Pricing Arrangements

- 6.54 The submission requested a Special Pricing Arrangement for the supply of ibrutinib to relapsed or refractory mantle cell lymphoma patients.

Table 14: Details of the Special Pricing Arrangement for ibrutinib proposed in the submission

Confidential		Published	
Effective AEMP	Effective DPMQ	List AEMP	List DPMQ
\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table F.1, p1, Section F of the submission

AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of ibrutinib on the PBS for the treatment of mantle cell lymphoma on the basis of high and uncertain cost-effectiveness at the requested price. The PBAC considered the magnitude of the clinical benefit was uncertain. This was because the comparator in the randomised trial (temsirolimus) was not relevant to Australian clinical practice, and the assumption that the efficacy of temsirolimus was the same as for R-CHOP, the nominated comparator for the submission, was based on naïve indirect comparisons. Further, the PBAC was of the view that a number of the assumptions used in the estimation of the cost-effectiveness were optimistic, and noted that the incremental cost-effectiveness ratio (ICER) was therefore likely to be higher than estimated in the submission.
- 7.2 The PBAC considered that there was a clinical need for additional effective and well tolerated treatments for relapsed/refractory mantle cell lymphoma.
- 7.3 The PBAC considered the nominated comparator of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) was appropriate, although noted other immunochemotherapy regimens may also be used in the treatment of relapsed/refractory mantle cell lymphoma. The PBAC agreed with the Pre-PBAC response that bendamustine with rituximab (BR) is commonly used in the first line setting, with R-CHOP commonly used in the relapsed/refractory setting.

- 7.4 The PBAC noted the efficacy of ibrutinib was compared with R-CHOP by using the randomised MCL-3001 trial which compared ibrutinib and temsirolimus, a naïve indirect comparison of the temsirolimus arm of MCL-3001 with studies assessing FR or R-FCM in the treatment of relapsed/refractory mantle cell lymphoma, and the assumption that R-CHOP is equivalent to FR and R-FCM with respect to efficacy. The PBAC considered this approach resulted in the magnitude of the incremental benefits being uncertain.
- 7.5 The PBAC noted the safety of ibrutinib was compared with R-CHOP by using the randomised MCL-3001 trial which compared ibrutinib and temsirolimus, and a naïve indirect comparison of the ibrutinib arm of MCL-3001 with studies assessing R-CHOP for the first-line treatment of mantle cell lymphoma. The PBAC noted and agreed with the arguments in the PSCR and Pre-PBAC response that using R-CHOP data from the first line setting potentially biased the comparison against ibrutinib as patients in the R-CHOP studies were younger, not previously treated, had more bone marrow reserve and may have had less co-morbidities.
- 7.6 The PBAC considered that the claim of superior comparative effectiveness over R-CHOP was reasonable based on the endpoint of progression free survival, however considered the magnitude of the benefit to be uncertain. The PBAC considered the uncertainty associated with the magnitude of the gain in overall survival was even greater because a statistically significant gain was not demonstrated in the MCL-3001 trial.
- 7.7 The PBAC considered that the claim of superior comparative safety over R-CHOP was not adequately supported by the data. The PBAC noted that ibrutinib appears to be associated with a reduced risk of neutropenia, and noted the emerging data suggesting ibrutinib may be associated with an increased risk of atrial fibrillation.
- 7.8 The PBAC considered that the costs associated with monitoring for atrial fibrillation should be included in the economic model and financial forecasts for any resubmission.
- 7.9 The PBAC considered that the ICER of \$75,000 - \$105,000 per QALY was high and based on optimistic assumptions, and therefore unlikely to give a reasonable estimate of the cost effectiveness of ibrutinib in the treatment of relapsed/refractory mantle cell lymphoma. The PBAC noted the following issues with the model:
- The non-conservative approach used to extrapolate the overall survival data from the trial. The PBAC agreed with the ESC that given a statistically significant gain in overall survival had not been demonstrated in the trial, that a conservative approach should be used when extrapolating the data, and that this would include the curves converging within the model time horizon and use of the unadjusted (intention to treat) results from the trial;
 - The use of a 15 year time horizon which was inconsistent with the poor prognosis of patients following relapse or becoming refractory, with an average overall survival of approximately two years;
 - The cost of subsequent therapy in the post-progression health state being lower for ibrutinib (\$██████) compared with R-CHOP (\$██████);
 - The magnitude of the disutilities applied for adverse events associated with R-CHOP; and

- The lower baseline utility applied to the R-CHOP arm (0.733) compared with the ibrutinib arm (0.79).
- 7.10 The PBAC noted the sensitivity analysis in the Pre-PBAC response (p3) where the effect of ibrutinib in delaying progression and death was assumed to cease at the end of the trial, and specifically the hazard rates for progression and death were assumed equal for ibrutinib and the comparator. The resulting ICER was \$105,000 - \$200,000 per QALY gained, which was only 5.2% higher than the base case ICER, and it was stated in the Pre-PBAC response that this analysis highlights the robustness of the model. The PBAC considered this analysis alone did not adequately test the robustness of the model, and noted additional sensitivity analyses in the submission and the commentary that suggested the ICER may exceed \$105,000 - \$200,000. Given the uncertain clinical gains and model issues noted above, the PBAC did not agree that the results of the economic model were robust.
- 7.11 The PBAC agreed with the DUSC that the number of patients likely to be treated with ibrutinib had been substantially overestimated and the resulting financial impact of listing ibrutinib on the PBS was overestimated. The PBAC noted that both the prevalent and incident populations were overestimated and the submission's estimate of the prevalent population (██████) was high relative to the number of people who are estimated to be living with mantle cell lymphoma in Australia (1,000).
- 7.12 The PBAC recommended that any resubmission should address the issues with the economic model noted in 7.9 and the financial estimates noted in 6.52 and 7.11, and therefore would need to be a major submission to allow for re-evaluation of the economic model and the financial forecasts.
- 7.13 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 is disappointed that the PBAC did not recommend ibrutinib for the treatment of relapsed or refractory Mantle Cell Lymphoma. Janssen agrees with the PBAC that there is a high clinical need for novel effective and well-tolerated therapies in relapsed and/or refractory Mantle Cell Lymphoma. Janssen intends to continue to engage with the PBAC and work towards a PBS listing.