

7.05 IBRUTINIB, Capsule 140 mg, Imbruvica[®], Janssen-Cilag Pty Ltd

1 Purpose of application

- 1.1 Section 85, Authority Required listing for ibrutinib for treatment of relapsed or refractory mantle cell lymphoma.
- 1.2 This was the second submission for ibrutinib for use in mantle cell lymphoma. The first submission was considered by the PBAC in November 2016.

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

Component	Description
Population	Relapsed or refractory mantle cell lymphoma after ≥ 1 prior therapy
Intervention	Ibrutinib; 560 mg (4 x 140 mg capsules) once daily until disease progression or unacceptable toxicity
Comparator	Immunochemotherapy, represented by R-CHOP for 6 to 8 cycles
Outcomes	PFS, OS, ORR, safety
Clinical claim	Ibrutinib is superior to R-CHOP in terms of comparative effectiveness (as assessed by PFS and OS). In terms of safety, ibrutinib is superior compared to active treatment with R-CHOP, and inferior compared to completed or discontinued R-CHOP in patients who remained progression free and were not receiving any further active treatment.

Source: Table 1.1-1, p17, Section 1 of the resubmission

ORR = overall response rate; OS = overall survival; PFS = progression free survival; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

- 1.3 The key components presented in the resubmission for ibrutinib were unchanged from the November 2016 submission, except for the clinical safety claim. This was modified from “ibrutinib was superior to rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) in terms of comparative safety” to “ibrutinib was superior compared to active treatment with R-CHOP, and inferior compared to completed or discontinued R-CHOP in patients who remained progression free and were not receiving any further active treatment.”

2 Requested listing

- 2.1 The proposed PBS listing was similar to that presented in the November 2016 submission. The listing was separated into initial and continuing treatment and included the November 2016 PBAC’s proposed changes.

Name, restriction, manner of administration and form	Maximum Qty (units)	No. of Rpts	Dispensed price for maximum quantity	Proprietary name and manufacturer
Ibrutinib, 140 mg, oral, capsules	120	5	Published: \$ [REDACTED] Effective (SPA): \$ [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
PBS Indication:	Mantle cell lymphoma
Restriction level/method	<input checked="" type="checkbox"/> Authority Required – Telephone
Initial treatment	
Clinical criteria	The condition must have relapsed or be refractory to at least one prior therapy AND Patient must have a WHO performance status score of 2 or less AND The treatment must be the sole PBS-subsidised therapy for this condition
Administrative advice	Special Pricing Arrangements apply
Continuing treatment phase	
Clinical criteria	The treatment must be the sole PBS-subsidised therapy for this condition AND Patient must have previously been issued with an authority prescription for this drug for this condition AND Patient must have stable or responding disease
Administrative advice	Special Pricing Arrangements apply

2.2 The resubmission proposed a [REDACTED] % reduction in the effective approved ex-manufacturer price (AEMP) from \$ [REDACTED] to \$ [REDACTED]. This resulted in a reduction in the effective dispensed price for the maximum quantity (DPMQ) from \$ [REDACTED] to \$ [REDACTED].

2.3 In the November 2016 submission the requested price for ibrutinib in relapsed or refractory mantle cell lymphoma was consistent with the recommended price per milligram for ibrutinib in relapsed or refractory chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL). This resulted in a higher effective price for the mantle cell indication as patients with mantle cell lymphoma require a higher dose (560 mg daily versus 420 mg daily). [REDACTED]

[REDACTED] However, the CLL/SLL indication was not considered cost-effective at this price and is subject to a Risk Share Arrangement (RSA) to further reduce the effective price.

3 Background

Registration status

3.1 TGA status: 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.

3.2 Ibrutinib is also TGA approved for:

- Adult patients with CLL/SLL who have received at least one prior therapy or adult patients with previously untreated CLL/SLL
- Patients with CLL/SLL with deletion 17p; and
- Adult patients with Waldenstrom’s macroglobulinaemia who have received at least one prior therapy, or in first-line treatment for patients unsuitable for chemo-immunotherapy.

Previous PBAC considerations

3.3 This was the second submission for ibrutinib for the treatment of relapsed or refractory mantle cell lymphoma. The first major submission was considered by the PBAC in November 2016.

3.4 A summary of the outstanding matters of concern to the PBAC are presented in Table 2.

Table 2: Summary of outstanding matters of concern

Component	Matter of concern (sourced from Nov 2016 Public Summary Document (PSD))	How the resubmission addressed it
Clinical Evidence		
Proposed PBS restriction	[Paragraphs 2.2 to 2.4] The requested restriction did not specify that patients must be relapsed or refractory to prior therapy, only that they must have received at least one prior therapy, nor did it include specific criteria to define progressive disease.	The resubmission adopted proposed changes into the amended restriction. This was appropriate.
Comparability of temsirolimus to the nominated comparator, R-CHOP	[Paragraph 7.4] The efficacy of ibrutinib was compared with R-CHOP by using a RCT that compared ibrutinib to temsirolimus and a naïve indirect comparison of the temsirolimus arm with studies assessing R-F or R-FCM in the treatment of R/R MCL, assuming that R-CHOP was equivalent to R-F and R-FCM. The PBAC considered this approach resulted in the magnitude of the incremental benefits being uncertain.	The resubmission used updated PFS and OS estimates in the comparisons between temsirolimus and R-F and R-FCM. In addition OS with temsirolimus was compared to OS observed in Australian and UK R/R MCL patients.
Efficacy claim	[Paragraph 7.6] The PBAC considered the claim of superior efficacy over R-CHOP was reasonable based on PFS, however the magnitude of benefit was uncertain. There was also uncertainty surrounding the magnitude of OS gains as the key RCT (MCL-3001) did not demonstrate a statistically significant benefit.	The resubmission presented updated PFS and OS data from the MCL-3001 trial. The difference in PFS remained [REDACTED]; the difference in OS remained [REDACTED]. The difference in OS became [REDACTED] when the temsirolimus arm was adjusted for crossover.

Component	Matter of concern (sourced from Nov 2016 Public Summary Document (PSD))	How the resubmission addressed it
Safety claim	[Paragraphs 7.5 and 7.7] A naïve indirect comparison of ibrutinib and R-CHOP used in 1 st -line MCL treatment was presented to assess safety. The PBAC considered that the claim of superior comparative safety over R-CHOP was not adequately supported by the data and that ibrutinib might be associated with an increased risk of AF.	The resubmission presented updated safety data from MCL-3001. The comparative safety claim of ibrutinib was divided into two parts: whilst patients are on R-CHOP treatment; and when R-CHOP treatment was completed/discontinued. The updated safety claims were reasonable. The risk of AF was not addressed in the safety analyses presented in the submission.
Economic model		
AF monitoring costs	[Paragraph 7.8] Monitoring costs associated with AF should be included in the economic model.	Monitoring costs were included in the economic model. This was appropriate.
ICER	[Paragraphs 7.9 and 7.10] The ICER of \$75,000/QALY - \$105,000/QALY (paragraph 7.9, November 2016 PSD) was considered high and based on optimistic assumptions and was therefore likely to be unreasonable. The economic model was not robust.	The resubmission presented a range of ICERs based on four scenarios – OS in the temsirolimus/R-CHOP arm adjusted for crossover using/not using the RPSFT method and the time horizon converging/not converging at 10 years.
Extrapolation of OS	[Paragraph 7.9] The PBAC considered that as statistically significant gains in OS had not been demonstrated a conservative approach when extrapolating the data should have been used, including OS curves converging within the model time horizon and use of unadjusted ITT results.	See above
Time horizon	[Paragraph 7.9] The 15 year time horizon was inconsistent with the average 2 year life expectancy of patients with R/R MCL.	Time horizon was extended to 17 years based on extrapolation of final analysis data. The ESC considered increasing the time horizon was not reasonable.
Cost of subsequent therapy	[Paragraph 7.9] It was inappropriate for post progression costs to differ between ibrutinib and R-CHOP (\$██████ vs \$██████) (paragraph 7.9, November 2016 PSD).	The cost of subsequent therapy was equal in both arms and applied to all patients who progressed. This was appropriate.
AE disutilities	[Paragraph 7.9] The magnitude of the disutilities applied for adverse events associated with R-CHOP.	Disutility values were revised downwards and applied, as per the November 2016 submission, to the R-CHOP arm only.
Baseline utilities	[Paragraph 7.9] A lower baseline utility was applied to the R-CHOP arm (0.733) compared with the ibrutinib arm (0.79).	The utilities remained unchanged.
Financial estimates		
Patient population	[Paragraphs 6.52 and 7.11] The PBAC considered the number of patients likely to be treated with ibrutinib was substantially overestimated. The prevalent and incident populations were overestimated because of: - the implausible assumption that all incident patients were alive two years after diagnosis and had relapsed; - the assumption that all prevalent patients would relapse; and - the method used to estimate the prevalent population.	The number of patients likely to be treated with ibrutinib was revised and: - a clinician survey was used to estimate the proportion of incident and prevalent patients who relapsed; - the method used to estimate the prevalent population was modified. These changes were reasonable, although the number of patients remained potentially overestimated.
AF monitoring costs	[Paragraph 7.8] Monitoring costs associated with AF should be included in the financial estimates.	AF monitoring costs were included. This was appropriate.

Source: November 2016 PSD and the resubmission

AE = adverse event; AF = atrial fibrillation; HMRN = Haematological Malignancy Research Network; ICER = incremental cost-effectiveness ratio; ITT = intention-to-treat; MCL = mantle cell lymphoma; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PFS = progression free survival; QALY = quality-adjusted life year; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RCT = randomised controlled trial; R-F = rituximab, fludarabine; R-FCM = rituximab, fludarabine, cyclophosphamide, mitozantrone; RPSFT = rank preserving structural failure time; R/R = relapsed or refractory; UK = United Kingdom

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

4 Population and disease

- 4.1 Mantle cell lymphoma is a rare and aggressive subtype of non-Hodgkin's 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. The proposed population was unchanged from the November 2016 submission and remained appropriate.

5 Comparator

- 5.1 As for the November 2016 submission, the nominated comparator was: the immunochemotherapy regimen of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP).
- 5.2 The PBAC had previously accepted that R-CHOP was the appropriate comparator (paragraph 7.3, November 2016 PSD). Although, the PBAC did note that other immunochemotherapy regimens may also be used in the treatment of relapsed or refractory mantle cell lymphoma.
- 5.3 The comparator in the clinical trial was temsirolimus, and like the November 2016 submission, the resubmission claimed temsirolimus represented R-CHOP in terms of efficacy.
- 5.4 In terms of safety, the resubmission again considered the use of R-CHOP in patients with newly diagnosed mantle cell lymphoma represented R-CHOP in patients with relapsed or refractory disease.

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 one individual and organisations (2) via the Consumer Comments facility on the PBS website. The comments outlined the high unmet need for effective treatments for relapsed/refractory mantle cell lymphoma. The comments described a range of benefits of treatment with ibrutinib

including fewer side effects, ease of administration, and slowing of disease progression for a longer period, without too much impact on quality of life. The comments also highlighted the high cost of the drug without PBS subsidy.

Clinical trials

- 6.3 As for the November 2016 submission, the resubmission was based on one head-to-head trial, MCL-3001, which compared ibrutinib to temsirolimus (N = 280). The resubmission presented data from the final analysis of MCL-3001 (the November 2016 submission used interim analysis data).
- 6.4 The efficacy and safety of ibrutinib was firstly compared to temsirolimus, using the results from MCL-3001.
- 6.5 To inform efficacy, a naïve indirect comparison was performed between the updated temsirolimus data from MCL-3001 and subgroups of relapsed or refractory mantle cell lymphoma patients who had received rituximab-containing immunochemotherapies, which were assumed to be equivalent to R-CHOP (Rummel 2016 and Forstpointner 2004). These studies were previously presented in the November 2016 submission.
- 6.6 The resubmission presented two new patient-based analyses of long-term overall survival in Australian (Opat 2016) and UK (Patmore 2016) mantle cell lymphoma patients. These data were compared to the temsirolimus overall survival data to support the claim that temsirolimus was at least as effective as current rituximab containing immunochemotherapy treatments.
- 6.7 To inform safety, a naïve indirect comparison was performed between the ibrutinib arm of MCL-3001 and R-CHOP in treatment naïve patients (Lenz 2005, Kluin-Nelemans 2012 and Robak 2015). An additional analysis, which compared the safety of ibrutinib at six months with R-CHOP, was presented in the resubmission. The resubmission proposed that the six-month safety data for ibrutinib more closely represented the duration of a course of R-CHOP. The evaluation considered this was reasonable.
- 6.8 Details of the trials and supplementary studies presented in the resubmission are provided in the table below.

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/Publication title	Publication citation
Direct randomised trial		
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. Interim clinical study report and final clinical study report. Dreyling M, Junczak W, Jerkeman M, et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, Phase 3 study.	11 September 2015; 1 May 2017. The Lancet 2016; 307: 770-778.
Supplementary randomised trials – proxies for efficacy of R-CHOP		
Forstpointner (2004)	Forstpointner R, Dreyling M, Repp R, et al. 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.	Blood 2004; 104(10): 3064-3071.
Rummel (2016)	Rummel M, Kaiser U, Basler C, et al. 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.	Lancet Oncology 2016; 17: 57-66.
Supplementary studies – proxies for efficacy of R-CHOP		
Opat (2016)	Opat S. Mantle cell lymphoma. Monash Health.	2016
Patmore (2016)	Patmore R, Smith A, Appleton S, et al. Mantle cell lymphoma management and outcome in the UK's population-based Haematological Malignancy Research Network. Abstract only.	American Society of Hematology – 58th meeting. 2016; 1112.
Supplementary randomised trials – safety of R-CHOP		
Lenz (2005)	Lenz G, Dreyling M, Hoster E, et al. 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).	Journal of Clinical Oncology 2005; 23(9): 1984-1992.
Kluin-Nelemans (2012)	Kluin-Nelemans H, Hoster E, Hermine O, et al. Treatment of older patients with mantle-cell lymphoma.	New England Journal of Medicine 2012; 367: 520-531.
Robak (2015)	Robak T, Huang H, Jie J, et al. Bortezomib-based therapy for newly diagnosed Mantle-cell lymphoma.	New England Journal of Medicine 2015; 372(10): 944-953.

Source: Table 2.12, p20 of the resubmission and compiled from Section 2 of the resubmission during evaluation
R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

6.9 The key features of the randomised trials and supplementary studies are summarised in the table below.

Table 4: Key features of the included evidence, ibrutinib versus R-CHOP

Trial	N	Design/duration of follow-up	Risk of bias	Patient population	Outcome	Used in economic evaluation
Ibrutinib versus temsirolimus						
MCL-3001	280	R, OL, MC [redacted] months	Unclear	R/R MCL	PFS, OS, Safety	Yes
Efficacy –R-CHOP						
Forstpointner (2004)	24 ^a	R*, OL, MC 18 months	Unclear	R/R MCL	ORR, PFS, OS, Safety	No
Rummel (2016)	23 ^b	R*, OL, MC 96 months	High	R/R MCL	PFS, OS, ORR, Safety	No
Opat (2016)	58	Retrospective analysis of registry data 2004-2015	High	MCL	OS	No
Patmore (2016)	327	Retrospective analysis of registry data 2006-2016	High	MCL	OS	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 ^d	R*, OL, MC 37 months	High	Newly diagnosed MCL; ≥ 60 years;	ORR, TTF, Safety	Yes
Robak (2015)	244 ^e	R*, OL, MC 40 months	Unclear	Newly diagnosed MCL; Stage II-IV	PFS, ORR, Safety	Yes

Source: Section 2 of the resubmission

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; R/R = relapsed or refractory; 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. Of the 47 who had MCL, 23 received rituximab, fludarabine 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

6.10 The risk of bias in MCL-3001 was unclear due to the open-label nature of the trial and the large differences in patient discontinuations between the trial arms due to adverse events ([redacted]% in the ibrutinib arm and [redacted]% in the temsirolimus arm) and refusing further treatment between the treatment arms ([redacted]% in the ibrutinib arm and [redacted]% in the temsirolimus arm).

6.11 As described in the November 2016 commentary, patients treated in the temsirolimus arm of the MCL-3001 trial were allowed to crossover after the Independent Review Committee (IRC) confirmed progression. At the final analysis, a total of [redacted] patients initially randomised to temsirolimus were exposed to ibrutinib.

Comparative effectiveness

6.12 Results from trial MCL-3001, which compared ibrutinib to temsirolimus, are provided in the following table.

Table 5: Results of progression free survival and overall survival from trial MCL-3001 (ITT population)

	Ibrutinib (n = 139)	Temsirolimus (n = 141)	Hazard ratio (95% CI)	
Progression free survival (investigator assessed)				
Median follow-up, months	█			
Patient status, n (%):				
Progressed or died	█	█		
Censored	█	█		
Median PFS, months (95% CI)	█	█	█	
Overall survival				
Median follow-up, months	█			
Patient status, n (%):				
Died	█	█		
Censored	█	█		
Crossover/subsequent ibrutinib	█	█		
Median OS, months (95% CI)	█	█	ITT	█
			RPSFT method	█
November 2016 submission				
Median follow-up, months	20.3	19.7		
Median PFS, months (95% CI)	█	█	0.43 (0.32, 0.58)	
Median OS, months (95% CI)	NE (18.6, NE)	21.3 (13.0, NE)	ITT	0.76 (0.53, 1.09)
			RPSFT method	█

Source: Tables 2.16-2.18, pp30-36, and Table 2.32, p63, Section 2 of the resubmission

CI = confidence interval; ITT = intention-to-treat; NE = not estimable; OS = overall survival; PFS = progression free survival; RPSFT = rank preserving structural failure time; **Bold** = statistically significant

6.13 At the final analysis of MCL-3001, the median follow-up was █ months in both the ibrutinib and temsirolimus arms. The median progression free survival was █ months for ibrutinib patients and 6.2 months for temsirolimus patients. This improvement was statistically significant (hazard ratio [HR] = █; 95% confidence interval (CI): █). The final analysis results were consistent with the interim analysis results presented in the November 2016 submission.

6.14 At the final analysis of MCL-3001, █ and █ patients had died in the ibrutinib and temsirolimus arms respectively. The median overall survival was █ in the ibrutinib arm (█ months) compared to the temsirolimus arm (█ months), █.

6.15 Consistent with the November 2016 submission, the difference in overall survival was █; however, the 95% confidence intervals (HR = █; 95% CI: █) had narrowed since the interim analysis (HR = 0.76; 95% CI: 0.53, 1.09). Although the survival analysis █ ibrutinib compared with temsirolimus, █ (and

MCL-3001 was not powered to detect a significant improvement in overall survival), uncertainty associated with the magnitude of the gain remained.

- 6.16 The resubmission stated that crossover, which allowed patients in the temsirolimus arm to receive ibrutinib following progression, resulted in an overestimated overall survival benefit for temsirolimus. Therefore, as per the November 2016 submission, the resubmission presented additional analyses adjusting for crossover. The resubmission stated a preference for the rank preserving structural failure time (RPSFT) method. During the evaluation this method was considered 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. The ESC noted patients who crossed over to ibrutinib had failed an additional line of therapy compared with patients initially randomised to ibrutinib and considered this may result in a reduced treatment effect in these patients. If this is the case, the RPSFT method would result in the ibrutinib treatment effect being overestimated. The resubmission, like the November 2016 submission, provided additional methods to adjust for crossover including the iterative parameter estimation (IPE) algorithm and the inverse probability of censoring weight (IPCW). The IPE method produced a similar result to the RPSFT method. The IPCW method produced results which were similar to the unadjusted results. The ESC noted the key assumption for the IPCW method is that all prognostic variables for crossing over are accounted for (i.e. there are no unmeasured confounders), and that the direction of bias is less certain with the IPCW method than the RPSFT method. The ESC noted there are many analytic choices when applying adjustments for crossover and these should be tested in sensitivity analyses.
- 6.17 The overall survival hazard ratio adjusted using the RPSFT method was [REDACTED] (HR = [REDACTED]; 95% CI: [REDACTED]).
- 6.18 The ESC considered that the primary clinical issue with the resubmission was the evidence basis for the clinical claim, i.e., the lack of direct or robust evidence to inform the comparative efficacy of ibrutinib with the selected comparator (R-CHOP) in the relevant patient population (relapsed and refractory mantle cell lymphoma). The ESC considered that the deliberations regarding the adjustment for crossover were secondary to the concerns around whether to accept the naïve indirect comparison of temsirolimus versus R-CHOP.
- 6.19 The resubmission presented a naïve comparison of progression free survival and overall survival outcomes for patients treated with temsirolimus from the final analysis of the MCL-3001 trial and patients treated with other immunochemotherapies.

Table 6: Comparison of efficacy between temsirolimus and immunochemotherapy

	Treatment	Median PFS, months (95% CI)	Median OS, months (95% CI)
MCL-3001 (final analysis)	Temsirolimus (n = 141)	6.2 (4.2, 7.8)	██████████
Rummel (2016)	R-F (n = 23)	4.7 (2.3, 11.2)	20.9 (10.6, 56.7)
Forstpointner (2004)	R-FCM (n = 24)	8	NE; 65% alive at 2 years
Opat (2016)	Various (n = 21)	NR	22.8
Patmore (2016)	Various (n = 109)	NR	~ 12 ^a

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-F = rituximab, fludarabine; R-FCM = rituximab, fludarabine, cyclophosphamide, mitozantrone

^a Based on visual assessment of Kaplan-Meier survival estimates

- 6.20 As in the November 2016 submission, the resubmission concluded that the efficacy of rituximab plus fludarabine (Rummel 2016) and rituximab, fludarabine, cyclophosphamide and mitozantrone (R-FCM) (Forstpointner 2004) were broadly similar to the efficacy of temsirolimus in patients with relapsed or refractory mantle cell lymphoma, based on progression free and overall survival outcomes.
- 6.21 Data from two retrospective analyses of registry data in Australia and the UK were presented by the resubmission to support the claim that temsirolimus was at least as effective as current treatments. The median overall survival for Australian patients with progressed mantle cell lymphoma (Opat 2016) was 22.8 months. This was comparable with the median overall survival for temsirolimus treated patients (██████████ months).
- 6.22 The results from Patmore (2016) suggested that UK patients had a significantly poorer outcome compared to temsirolimus patients in the MCL-3001 trial, with a median overall survival of approximately 12 months following second- or third-line therapy.
- 6.23 The resubmission concluded that these comparisons demonstrated that temsirolimus was comparable to R-CHOP in terms of efficacy. No evidence was provided to support the assumption that R-CHOP was comparable to immunochemotherapies in terms of efficacy. Furthermore, the additional data from Opat (2016) and Patmore (2016) was based on naïve retrospective analyses of registry data which included heterogeneous non-trial based patients, who may have a poorer prognosis compared with those included in the MCL-3001 trial.
- 6.24 The ESC noted that the updated clinical data presented in the resubmission from the final analysis of MCL-3001 were consistent with the interim analysis results in the previous submission, and that the difference in overall survival between ibrutinib and temsirolimus ██████████. The ESC therefore considered that the updated data did not change its concern that the magnitude of benefit with ibrutinib over temsirolimus was uncertain.

Comparative harms

- 6.25 The resubmission presented new safety data from MCL-3001 for ibrutinib – safety at six months and at final analysis.

- 6.26 The resubmission proposed that the six-month safety data for ibrutinib more closely represented the duration of a course of R-CHOP and the final analysis data more closely represented the comparative safety of ibrutinib and patients no longer receiving R-CHOP treatment. The evaluation considered this was reasonable.
- 6.27 A naïve indirect comparison of the overall safety profile of ibrutinib and temsirolimus from MCL-3001 (at six months and final analysis) and R-CHOP (from Robak 2015) are presented below.

Table 7: Naïve comparison of safety between ibrutinib, temsirolimus and R-CHOP

	MCL-3001 – 6 months		MCL-3001 – final analysis		Robak (2015)
	Ibrutinib (N = 139)	Temsirolimus (N = 139)	Ibrutinib (N = 139)	Temsirolimus (N = 139)	R-CHOP (N = 242)
Median treatment duration	-	-	██████	██████	3.7 months
Any TE AE	██████	██████	██████	██████	238 (98%)
Grade ≥ 3	██████	██████	██████	██████	206 (85%)
Drug related	██████	██████	██████	██████	226 (93%)
Any TE SAE	██████	██████	██████	██████	72 (30%)
Drug related	██████	██████	██████	██████	50 (21%)
AE resulting in discontinuation	██████	██████	██████	██████	17 (7%)
AE resulting in death	██████	██████	██████	██████	12 (5%)
Additional AEs					
Atrial fibrillation (Grade ≥ 3)	██████	██████	██████	██████	NR

Source: Table 2.35, p81, Section 2 of the resubmission; Tables TSFAE39A and TSFAE41A, pp899-920 of interim CSR

AE = adverse events; CSR = clinical study report; NR = not reported; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; SAE = serious adverse event; TE = treatment emergent

- 6.28 Compared to temsirolimus, ibrutinib patients had a lower incidence of any Grade 3 or higher adverse event, any drug related adverse event, any drug related serious adverse event, and any adverse event resulting in discontinuation from the trial at both six months and at the final analysis of MCL-3001.
- 6.29 Based on the naïve indirect comparison, the rates of any Grade 3 or higher adverse events, drug related adverse events and serious drug related adverse events were lower for ibrutinib patients than R-CHOP patients at six months. This was despite ibrutinib patients being relapsed or refractory and R-CHOP patients being newly diagnosed. Although difficult to quantify, as the comparison was naïve, the PBAC had previously agreed with the resubmission’s argument that using R-CHOP data sourced from a newly diagnosed population 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 (paragraph 7.5, November 2016 PSD).
- 6.30 The PBAC had previously noted that emerging data suggested that ibrutinib was associated with an increased risk of atrial fibrillation (paragraph 7.7, November 2016 PSD). Ibrutinib patients at six months and at the final analysis of MCL-3001 had higher rates of atrial fibrillation than temsirolimus patients. Atrial fibrillation was not reported in the R-CHOP trial (Robak 2015). The Pre-Sub-Committee Response (PSCR) (p2) stated the data available from MCL-3001 are the longest-term safety data

available for ibrutinib (or any other therapy) in RR MCL, and the incidence of atrial fibrillation (5% for ibrutinib versus 1.4% for temsirolimus) was similar to the rates reported for the pooled relapsed refractory MCL and chronic lymphocytic leukaemia (CLL) trials (6.5% for ibrutinib versus 1.6% for comparator treatments). The PSCR further noted (p3) that most of the atrial fibrillation events were managed through dose reductions and interruptions rather than treatment discontinuations or use of additional therapies. The ESC noted the incidence of atrial fibrillation with ibrutinib when used outside of the clinical trial setting is currently unknown.

- 6.31 The pre-PBAC response (p2) referred to a systematic review and meta-analysis of the risk of atrial fibrillation with ibrutinib across a range of conditions (Leong 2016).¹ The meta-analysis found that, over median follow-ups of up to 26 months, the pooled rate of atrial fibrillation was 3.3 (95% CI: 2.5-4.1) per 100 person-years in patients treated with ibrutinib, versus 0.84 (95% CI: 0.32-1.6) in patients treated with other therapies. The pre-PBAC response stated that most atrial fibrillation events occur early in therapy and are mild to moderate in severity.
- 6.32 The most common adverse events associated with ibrutinib were diarrhoea (■%), fatigue (■%) and cough (■%). The most common serious adverse events associated with ibrutinib were pneumonia (■%) and atrial fibrillation (■%).
- 6.33 The ESC noted, when reviewing the submission for ibrutinib for first-line CLL, that there is an increased risk of bleeding in patients taking ibrutinib and it is contraindicated in patients with high bleeding risk including those who are on anticoagulant medications. Haemorrhage and bruising are listed as very common treatment-emergent adverse drug reactions in the ibrutinib Product Information, with other common events being subdural haematoma, petechiae, epistaxis. The incidence is decreased in subsequent clinical trials including RESONATE-2, likely due to stringent exclusion criteria of patients with high bleeding risk.

Benefits and harms

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

¹ Leong, D. et al. (2016). The risk of atrial fibrillation with ibrutinib use: a systematic review and meta-analysis. *Blood*, 128(1), 138-140. Accessed November 08, 2017.

Table 8: Benefits and harms: ibrutinib and immunochemotherapy/R-CHOP

EFFICACY								
	Ibrutinib	Temsirolimus	Immunochemotherapy	Absolute difference	HR (95% CI)			
Progression free survival – median (months)								
MCL-3001-final analysis Events, n/N (%) ^a Median PFS, months	██████████ ██████████	██████████ ██████████	█	█ █	██████████			
Rummel (2016) Median PFS, months	-	-	R-F = 4.7 (2.3, 11.2)	NC	NC			
Forstpointner (2004) Median PFS, months	-	-	R-FCM = 8	NC	NC			
Overall survival – median (months)								
MCL-3001 Events, n/N (%) ^a Median OS, months	██████████ ██████████	██████████ ██████████	█	█ █	██████████			
Rummel (2016) Median OS, months	-	-	R-F = 20.9 (10.6, 56.7)	NC	NC			
Opat (2016) Median OS, months	-	-	Various = 22.8	NC	NC			
Patmore (2016) Median OS, months	-	-	Various = -12	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 - 6 months ^b	██████	██████	█	██████████	█	█	█	██████████
MCL-3001 - final analysis	██████	██████	█	██████████	█	█	█	██████████
Robak (2015)	-	-	162/242	NC	-	-	67	NC
Kluin-Nelemans (2012)	-	-	149/249	NC	-	-	60	NC
Febrile neutropenia (≥ Grade 3)								
MCL-3001 - 6 months ^b	██████	██████	█	██████████	█	█	█	██████████
MCL-3001 - final analysis	██████	██████	█	██████████	█	█	█	██████████
Robak (2015)	-	-	33/242	NC	-	-	14	NC
Kluin-Nelemans (2012)	-	-	42/249	NC	-	-	17	NC
Atrial Fibrillation (≥ Grade 3)								
MCL-3001 - 6 months ^b	██████	██████	█	██████████	█	█	█	██████████
MCL-3001 - final analysis	██████	██████	█	██████████	█	█	█	██████████
Robak (2015)	-	-	-	-	-	-	-	-
Kluin-Nelemans (2012)	-	-	-	-	-	-	-	-

Source: Table 2.16 and 2.18, pp30-36, and Table 2.35, p80, Section 2 of the resubmission; Tables TSFAE02 and TSFAE06, pp74-113 of final CSR; Tables TSFAE39A and TSFAE41A, pp899-920 of interim CSR; Kluin-Nelemans (2012); Robak (2015); Patmore (2016); Opat

(2016); Forstpointner (2004); and Rummel (2016)

CI = confidence interval; CSR = clinical study report; HR = hazard ratio; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; NC = not calculable; 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, temsirolimus arm = 3 months; Robak = 3.7 months; Kluij-Nelemans = 5.0 months

^a

^b Any grade adverse event reported

- 6.35 The resubmission did not present any evidence of the efficacy of R-CHOP in patients with relapsed or refractory mantle cell lymphoma. Therefore, it was not possible to compare ibrutinib with R-CHOP in terms of efficacy in the proposed patient population.
- 6.36 The resubmission did not present any evidence of the safety of R-CHOP in patients with relapsed or refractory mantle cell lymphoma. Therefore, it was not possible to compare ibrutinib with R-CHOP in terms of safety in the proposed patient population.
- 6.37 When compared to temsirolimus, which was not the nominated comparator, but which provided the data used in the economic model, on the basis of the direct evidence presented by the resubmission, for every 100 patients treated with ibrutinib there would be approximately [REDACTED] patients who remained progression-free over a median duration of follow-up of [REDACTED]; [REDACTED] [REDACTED] in overall survival between the two groups.
- 6.38 When compared to temsirolimus, which was not the nominated comparator, on the basis of the evidence presented in the resubmission, for every 100 patients treated with ibrutinib:
- Approximately [REDACTED] patients would experience atrial fibrillation over a duration of follow-up of six months; and
 - Approximately [REDACTED] patients would experience atrial fibrillation over a median duration of follow-up of [REDACTED] months.

Interpretation of clinical evidence

Ibrutinib versus temsirolimus

- 6.39 The resubmission described ibrutinib as superior in terms of comparative effectiveness and superior in terms of comparative safety over temsirolimus.
- 6.40 The final analysis data from the MCL-3001 trial supported the trend of superiority of ibrutinib over temsirolimus. However, as in the November 2016 submission, there remained uncertainty associated with the magnitude of benefit as:
- although ibrutinib again showed statistically significant gains in progression free survival (HR = [REDACTED]; 95% CI: [REDACTED]), the overall survival analysis did not demonstrate a statistically significant improvement (HR = [REDACTED]; 95% CI: [REDACTED]); and

- overall survival gains [REDACTED]

6.41 The evaluation considered the claim of superior safety of ibrutinib compared to temsirolimus was adequately supported by the final analysis results from the MCL-3001 trial. Ibrutinib demonstrated a [REDACTED] incidence, over a median follow-up [REDACTED] months, of Grade 3 or higher adverse events, drug related adverse events, drug related serious adverse events and adverse events resulting in discontinuation from the trial. Ibrutinib patients did experience a non-statistically significant increase in the rates of atrial fibrillation. Longer-term safety data comparing ibrutinib and temsirolimus was not provided.

Ibrutinib versus R-CHOP

6.42 The resubmission described ibrutinib as superior to R-CHOP in terms of comparative efficacy and superior in terms of comparative safety when compared to patients on active treatment with R-CHOP, and inferior in terms of comparative safety when compared to patients who have completed or discontinued R-CHOP treatment but remained progression free.

6.43 As per the November 2016 submission, the resubmission's clinical claim was based on a naïve indirect comparison between temsirolimus and immunochemotherapy regimens, which were used as a proxy for R-CHOP. The evaluation considered the claim of superior effectiveness might not be adequately supported as:

- no evidence was provided to support the assumption that R-CHOP was comparable to rituximab plus fludarabine or R-FCM;
- the indirect comparison between temsirolimus and the immunochemotherapies had no common comparator; and
- although the additional data from Opat (2016) and Patmore (2016) suggested that temsirolimus might be at least as effective as current treatments at prolonging life in relapsed or refractory mantle cell lymphoma patients, the data were based on naïve, indirect retrospective analyses of heterogeneous patients and compared trial and non-trial based patient populations.

6.44 The evaluation considered the claim that ibrutinib was associated with superior comparative safety compared to active treatment with R-CHOP was reasonable. However, as in the November 2016 submission, the results were based on a naïve indirect comparison between relapsed or refractory ibrutinib patients and newly diagnosed R-CHOP patients and should be interpreted with caution.

6.45 The evaluation considered the claim that ibrutinib was associated with inferior comparative safety compared to completed or discontinued R-CHOP treatment was reasonable. However, the evaluation considered that the resubmission had not provided any new long-term safety data for ibrutinib and did not address the PBAC's concerns regarding the longer-term safety of ibrutinib, particularly the emerging evidence that it may be associated with atrial fibrillation. The pre-PBAC response (p2) disagreed stating that safety data from the longer-term follow-up of MCL-3001 had been provided (presented in Table 7, above), albeit this was versus temsirolimus.

Further, the pre-PBAC response had provided additional information on the risk of atrial fibrillation (refer to paragraph 6.31).

- 6.46 The PSCR (p2) acknowledged the limitations of the evidence presented by the resubmission, but reiterated that these data were the best available evidence of the efficacy and safety of any immunochemotherapy regimen in relapsed or refractory mantle cell lymphoma. The PSCR stated that there are unlikely to be any clinical trials conducted with R-CHOP or other immunochemotherapies in relapsed or refractory mantle cell lymphoma in the future as the standard of care globally is now targeted therapies such as ibrutinib. The PSCR argued that the PBAC will face these same issues in the quality of the evidence when considering the PBS listing of any new therapy for relapsed or refractory mantle cell lymphoma.
- 6.47 The ESC considered, despite the additional clinical data presented in the resubmission, that the uncertainty around the magnitude of benefit, and safety, of ibrutinib compared to R-CHOP remained, due to the inherent methodological issues (low internal and external validity) associated with the naïve indirect comparison of ibrutinib versus R-CHOP, via the naïve indirect comparison between temsirolimus and immunochemotherapy regimens.
- 6.48 The PBAC considered that the claim of superior comparative effectiveness of ibrutinib versus R-CHOP was reasonable, but that the magnitude of the incremental benefit remained uncertain due to the limitations of the naïve indirect comparison.
- 6.49 The PBAC considered the claim that ibrutinib was associated with superior comparative safety versus active treatment with R-CHOP was reasonable.

Economic analysis

- 6.50 As per the November 2016 submission, the resubmission presented a partitioned survival economic evaluation, based on the randomised trial (MCL-3001) that compared ibrutinib with temsirolimus, and naïve comparisons between temsirolimus and other rituximab-based regimens that were used as a proxy for the main comparator, R-CHOP. The type of economic evaluation presented was a cost-utility analysis.
- 6.51 The table below summarises the key components of the economic evaluation.

Table 9: Summary of model structure and rationale

Component	Summary
Time horizon	17 years in the model base case (versus ■ months OS follow-up in MCL-3001) – Increased from 15 years in the November 2016 submission.
Outcomes	LYs and QALYs
Method used to generate results	Decision analytic model that used the area under the curve methods to estimate PFS and OS (partitioned survival analysis).
Health states	Progression free, progressed and dead
Utilities	Trial based (MCL-3001)
Cycle length	30 days (1 month) with half-cycle correction
Transition probabilities	PFS: KM estimates from MCL-3001 were used until 10% of patients remained at risk. Beyond this exponential extrapolation was applied – Updated using final analysis data. OS: KM estimates from MCL-3001 were used until 20% of patients remained at risk. Beyond this exponential extrapolation was applied – Updated using final analysis data.
Discount rate	5% for costs and outcomes

Source: Section 3 of the resubmission

KM = Kaplan-Meier; LY = life year; OS = overall survival; PFS = progression free survival; QALY = quality-adjusted life year

6.52 The resubmission presented a scenario analysis to generate a range of incremental cost-effectiveness ratios (ICERs) to demonstrate the cost-effectiveness of ibrutinib in relapsed or refractory mantle cell lymphoma. The scenarios presented explored the impact of treatment crossover in the temsirolimus/R-CHOP arm and converging of the overall survival curves at 10 years. The resubmission stated that by providing an ICER range the uncertainty around the cost-effectiveness was quantified.

6.53 The four scenarios used to generate the ICER range are outlined in the table below.

Table 10: Scenarios used in the economic evaluation to generate the range of ICERs

	Scenario 1	Scenario 2	Scenario 3	Scenario 4
OS convergence	No, lifetime = 17 years	Yes, at 10 years	No, lifetime = 17 years	Yes, at 10 years
OS adjustment due to comparator switching	Yes, RPSFT method	Yes, RPSFT method	No, ITT population	No, ITT population

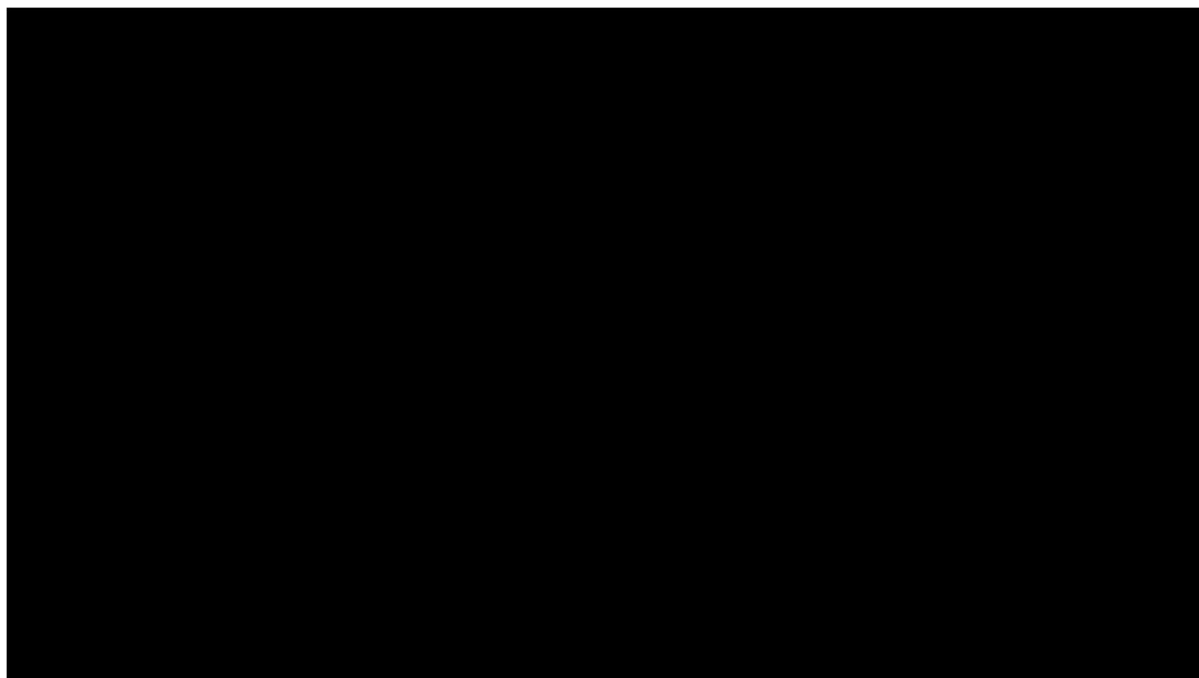
Source: Table 3.3, p12, Section 3 of the resubmission

ICER = incremental cost-effectiveness ratio; ITT = intention-to-treat; OS = overall survival; RPSFT = rank preserving structural failure time

6.54 The ESC considered that Scenario 4 was most consistent with the PBAC's recommendations from November 2016.

6.55 Figure 1 presents the progression free survival transitions used in the economic model.

Figure 1: PFS transitions used in the economic model – Kaplan-Meier estimates from MCL-3001 and exponential extrapolation



Source: Figure 3.8, p26, Section 3 of the resubmission

COMP = comparator (R-CHOP); FU = follow-up; IBR = ibrutinib; KM = Kaplan-Meier; PFS = progression free survival; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

6.56 Figure 2 presents the overall survival transitions used in the economic model. The left panel shows the overall survival curves adjusted for crossover in the temsirolimus/R-CHOP arm using the RPSFT method for the lifetime horizon (17 years) and converging at 10 years (Scenarios 1 and 2). The right panel shows the unadjusted overall survival curves for the lifetime horizon (17 years) and converging at 10 years (Scenarios 3 and 4).

Figure 2: OS curves with and without convergence at 10 years: Left panel - RPSFT method adjusted model (Scenarios 1 and 2); and Right panel - the ITT population model (Scenarios 3 and 4)



Source: Figure 3.12, p35, Section 3 of the resubmission and created during the evaluation using Ibrutinib – RR MCL – Model Updated Follow-Up.xlsx Excel file

COMP = comparator (R-CHOP); FU = follow-up; IBR = ibrutinib; KM = Kaplan-Meier; OS = overall survival; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RPSFT = rank preserving structural failure time

6.57 The ESC noted that the ibrutinib treatment effect would be overestimated when using the RPSFT adjustment method if the survival of patients treated with ibrutinib following temsirolimus (i.e. those who crossed over) was shorter than the survival for patients randomised to ibrutinib (see paragraph 6.14). The ESC noted that the IPCW analysis produced the most conservative adjusted estimate of treatment effect. Use of the IPCW adjusted estimates in the economic model rather than the RPSFT estimates increased the ICER to \$75,000 - \$105,000 per QALY gained for scenario 1 (17 year time horizon without convergence) and to \$105,000 - \$200,000 per QALY gained for scenario 2 (convergence at 10 years).

6.58 The ESC noted for the scenarios where convergence was not applied that a persistent treatment effect was assumed over time. The ESC considered this may not be appropriate, especially for the period when patients are no longer treated with ibrutinib.

6.59 The ESC noted both PFS and OS were extrapolated by fitting exponential functions to the trial data despite other functions having lower AICs. The ESC noted that the log-normal model has the lowest AIC for both the ITT and RPSFT analyses. The pre-PBAC response (p3) stated that the exponential function was chosen because it had the leanest tail and was the most conservative function for Scenario 4.

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

Table 11: Key drivers of the model

Description	Method/Value	Impact
PFS and OS in the R-CHOP arm	Efficacy of R-CHOP was assumed to be the same as the efficacy of temsirolimus in MCL-3001	Unknown; but likely to favour ibrutinib
Time horizon	The time horizon was extrapolated to 17 years (compared to 15 years in the November 2016 submission) in Scenarios 1 and 2, whereas overall survival was converged at 10 years in Scenarios 3 and 4.	High; favours ibrutinib
Adjustment for crossover and OS gains	The difference in overall survival in the clinical trial [REDACTED]. The RPSFT method was used to adjust for crossover in the temsirolimus arm. This resulted in [REDACTED].	High; favours ibrutinib
PFS utilities	Higher utilities were applied to ibrutinib patients (0.790) than R-CHOP patients (0.733) in the progression free health state	High; favours ibrutinib
Disutilities due to adverse events	Disutilities associated with adverse events were applied to R-CHOP patients only	Moderate; favours ibrutinib

Source: Section 3 of the resubmission

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

6.61 The PBAC previously considered that the 15 year time horizon presented in the November 2016 submission was inconsistent with the poor prognosis of patients with relapsed or refractory mantle cell lymphoma of approximately two years (paragraph 7.9 November 2016 PSD). The resubmission extended the time horizon to 17 years in Scenarios 1 and 2 based on the final analysis results from MCL-3001, which was

optimistic. Convergence of overall survival at 10 years in Scenarios 3 and 4 provided more conservative analyses.

6.62 As in the November 2016 submission, a lower baseline utility was applied to patients treated with R-CHOP in the progression free health state (0.733) compared with ibrutinib treated patients (0.790). The PBAC had previously noted this as an issue within the model to be addressed (paragraph 7.9, November 2016 PSD). The utility values applied in the model were unchanged in the resubmission. The PSCR (p3) argued that a higher baseline utility for ibrutinib is justified by the significant improvement in the FACT-Lym subscale compared with temsirolimus and this is noted to reflect faster recovery and greater improvement in lymphoma symptoms and hence quality of life with ibrutinib. The ESC noted the evidence may support the application of a higher utility to patients receiving ibrutinib, however, considered that the magnitude and duration of such effects are uncertain. The ESC considered that a reasonable approach, in light of this uncertainty, might be to apply an increased utility value for ibrutinib (0.79) over the first 8 cycles with the same utility value (0.733) after cycle 8. The pre-PBAC response (p3) disagreed with this approach, stating that the higher baseline utility with ibrutinib (which it stated was likely due to a greater improvement in lymphoma symptoms with ibrutinib) was unrelated to, and longer than, the duration of treatment with R-CHOP. Further, the pre-PBAC response argued that there was a correlation between lymphoma symptoms (FACT-Lym) and EQ-5D data from MCL-3001. However, the PBAC agreed with the ESC that the magnitude and duration of the effect are uncertain.

6.63 As per the November 2016 submission, the resubmission applied disutilities for specific adverse events to patients in the R-CHOP arm of the economic model only. However, the magnitude of these disutilities was reduced and the duration of time they were applied in the economic model was adjusted to address the concerns raised by the PBAC (paragraph 7.9, November 2016 PSD).

6.64 The disutilities used in the resubmission and how these compared to the November 2016 submission are presented below.

Table 12: Comparison of adverse event disutilities applied in the November 2016 submission and resubmission

Adverse event	November 2016 submission	November 2017 resubmission	% reduction
≥ Grade 3 neutropenia	-0.50 (cycle 1 only)	-0.23 (cycle 1 only)	54.0%
≥ Grade 3 febrile neutropenia	-0.49 (cycle 1 only)	-0.22 (cycle 1 only)	55.1%
≥ Grade 3 alopecia	-0.17 (cycles 1-8)	-0.09 (cycles 2-8)	47.1%
Any Grade fatigue	-0.49 (cycles 1-8)	-0.20 (cycles 2-8)	59.2%
Any grade peripheral neuropathy	-0.14 (cycles 1-8)	-0.115 (cycles 2-8)	17.9%

Source: Table 3.13, p48, Section 3 of the resubmission

6.65 The disutility decrements were applied additively. In the November 2016 submission the resulting utility values applied in the first and second cycles for progression free patients were 0.73 and 0.79 respectively for ibrutinib and 0.03 and 0.38 for R-CHOP; the ESC considered these differences to be implausible. In the resubmission the utility values applied for R-CHOP the first and second cycles were 0.616 and 0.609, which were more reasonable.

6.66 The ESC noted, although the disutilities applied in the resubmission were reduced compared with the November 2016 submission, that they are still potentially overestimated when compared with the utility data from the trial (0.790 for ibrutinib and 0.716 for temsirolimus for patients progression free).

6.67 The ESC noted more detailed utility data from the trial may provide more certainty regarding the application of treatment specific utility values. For example, information regarding the timing of data collection and the corresponding response rates, including response rates for patients with and without recorded adverse events, may be useful.

6.68 The results of the stepped economic evaluation for the four scenarios are presented below.

Table 13: Incremental health outcomes obtained in the economic evaluation (discounted)

	Costs			Health outcomes			ICER
	Ibrutinib	R-CHOP	Increment	Ibrutinib	R-CHOP	Increment	
Step 1: Trial based economic evaluation (RPSFT adjusted)							
MCL-3001 Time horizon: 47 months	██████	██████	██████	██████	██████	██████	██████
Step 1: Trial based economic evaluation (ITT population)							
MCL-3001 Time horizon: 47 months	██████	██████	██████	██████	██████	██████	██████
Step 2: Modelled lifetime economic evaluation (17 versus 10 year time horizon)							
Scenario 1: no convergence; RPSFT adjusted	██████	██████	██████	██████	██████	██████	██████
Scenario 2: OS convergence; RPSFT adjusted	██████	██████	██████	██████	██████	██████	██████
Scenario 3: No convergence; ITT population	██████	██████	██████	██████	██████	██████	██████
Scenario 4: OS convergence; ITT population	██████	██████	██████	██████	██████	██████	██████
November 2016 submission							
Base case	██████	██████	██████	██████	██████	██████	██████

Source: Tables 3.24 and 3.25, pp69-70, and Tables 3.26 and 3.27, pp73-74, Section 3 of the resubmission; Ibrutinib – RR MCL Model Updated Follow-Up.xlsx Excel file; and calculated during evaluation (corrected for % of R-CHOP patients experiencing AEs and for an incorrect cell linkage when calculating the R-CHOP life years)

AE = adverse event; ICER = incremental cost-effectiveness ratio; LY = life year; OS = overall survival; ITT = intention to treat; QALY = quality-adjusted life year; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RPSFT = rank preserving structural failure time

6.69 The four scenarios presented by the resubmission suggested that ibrutinib resulted in an incremental life year gain of between ██████ and ██████ and an incremental quality-adjusted life year (QALY) gain of ██████ to ██████. The incremental cost-effectiveness ratio

(ICER) for ibrutinib ranged from \$75,000 - \$105,000 in Scenario 1 to \$105,000 - \$200,000 in Scenario 4 per QALY gained, a difference of \$ [REDACTED].

6.70 Scenario 1 was most similar to the base case presented in the November 2016 submission, which presented an ICER of \$75,000/QALY - \$105,000/QALY and an incremental cost per life year of \$105,000 - \$200,000. The ICER in Scenario 1, \$75,000 - \$105,000, was lower than that presented in the November 2016 submission primarily due to the lower proposed price for ibrutinib.

6.71 The ESC considered that Scenario 4 (overall survival convergence at 10 years, no adjustment for crossover) was the most consistent with the PBAC’s recommendations based on the November 2016 submission. This scenario presented an ICER of \$105,000 - \$200,000per QALY gained. The ESC considered the cost per QALY gained (Scenario 4) still reflects the following optimistic assumptions:

- Application of exponential extrapolation curves with convergence at 10 years is not necessarily a conservative approach (the other scenarios are not plausible). The pre-PBAC response (p3) stated that the exponential function was chosen as it had the leanest tail and was the most conservative function when Scenario 4 was applied. However, the PBAC considered that the issue - that convergence of survival curves at 10 years was not necessarily conservative - remained given the poor prognosis of patients with relapsed or refractory mantle cell lymphoma.
- Significant utility decrements applied to the comparator arm and utility differences between the treatment arms while patients remain progression-free. Assigning the same progression-free utilities for both treatment arms increased the ICER to \$105,000 - \$200,000per QALY gained. Assigning the same progression-free utilities for both treatment arms and removing the treatment period utility decrements for the comparator arm increased the ICER to \$105,000/QALY - \$200,000/QALY.

6.72 Table 14 presents the key sensitivity analyses for the four scenarios presented in the economic evaluation.

Table 14: Results of the key sensitivity analyses for the economic evaluation

	Incremental costs	Incremental QALY	ICER
Scenario 1: no convergence (17 year time horizon), RPSFT method adjusted			
Base case	[REDACTED]	[REDACTED]	[REDACTED]
Adjustments for crossover (base case = RPSFT method)			
ITT (unbiased; temsirolimus censored at amendment)	[REDACTED]	[REDACTED]	[REDACTED]
IPE	[REDACTED]	[REDACTED]	[REDACTED]
IPCW	[REDACTED]	[REDACTED]	[REDACTED]
Baseline utility - progression free (base case: ibrutinib = 0.790; R-CHOP = 0.733)			
Baseline in both arms = 0.733	[REDACTED]	[REDACTED]	[REDACTED]
Adverse event disutilities			
All disutilities = 0	[REDACTED]	[REDACTED]	[REDACTED]
Scenario 2: convergence at 10 years, RPSFT method adjusted			
Base case	[REDACTED]	[REDACTED]	[REDACTED]

	Incremental costs	Incremental QALY	ICER
Overall survival convergence (base case = 10 years)			
5 years	██████	██████	██████
7 years	██████	██████	██████
Adjustments for crossover (base case = RPSFT method)			
ITT (unbiased; temsirolimus censored at amendment)	██████	██████	██████
IPE	██████	██████	██████
IPCW	██████	██████	██████
Baseline utility - progression free (base case: ibrutinib = 0.790; R-CHOP = 0.733)			
Baseline in both arms = 0.733	██████	██████	██████
Adverse event disutilities			
All disutilities = 0	██████	██████	██████
Baseline utility in both arms = 0.733; all disutilities = 0	██████	██████	██████
Convergence at 5 years; baseline utility in both arms = 0.733; all disutilities = 0	██████	██████	██████
Scenario 3: no convergence (17 year time horizon), unadjusted ITT population			
Base case	██████	0.66	██████
Baseline utility - progression free (base case: ibrutinib = 0.790; R-CHOP = 0.733)			
Baseline in both arms = 0.733	██████	0.56	██████
Adverse event disutilities			
All disutilities = 0	██████	0.61	██████
Scenario 4: convergence at 10 years, unadjusted ITT population			
Base case	██████	0.53	██████
Overall survival convergence (base case = 10 years)			
5 years	██████	0.43	██████
7 years	██████	0.48	██████
Baseline utility - progression free (base case: ibrutinib = 0.790; R-CHOP = 0.733)			
Baseline in both arms = 0.733	██████	0.43	██████
Adverse event disutilities			
All disutilities = 0	██████	0.48	██████
Baseline utility in both arms = 0.733; all disutilities = 0	██████	0.38	██████
Convergence at 5 years; baseline utility in both arms = 0.733; all disutilities = 0	██████	0.28	██████

Source: Table 3.29, p77, Section 3 of the resubmission; Ibrutinib – RR MCL Model Updated Follow-Up.xlsx Excel file; and conducted during the evaluation (corrected for % of R-CHOP patients experiencing AEs and for an incorrect cell linkage when calculating the R-CHOP life years)

ICER = incremental cost-effectiveness ratio; ITT = intention-to-treat; QALY = quality-adjusted life year; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RPSFT = rank-preserving structural failure time

The redacted table shows ICERs in the range of \$45,000/QALY to more than \$200,000/QALY.

6.73 The ICER for each scenario was most sensitive to applying the same baseline utility to ibrutinib and R-CHOP patients in the progression free health state (0.733). Multivariate analyses which combined convergence of overall survival, a common baseline utility in the progression free health state and no disutilities due to adverse events resulted in large changes to the ICERs, particularly when the unadjusted intention-to-treat population was used (Scenario 4).

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

- 6.74 The average cost of ibrutinib was estimated to be \$ [REDACTED] per cycle/month (30 days), based on the proposed effective 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 (17 year time horizon), the average length of treatment was [REDACTED] months. The total cost per patient per course was estimated to be \$ [REDACTED].
- 6.75 In the November 2016 submission, the average cost per cycle/month for ibrutinib was \$ [REDACTED], and the total cost per patient was estimated to be \$ [REDACTED] (average length of treatment was 23.4 months, dose intensity was [REDACTED]%).
- 6.76 The average cost of R-CHOP was estimated to be \$ [REDACTED] per cycle, based on the DPMQs of each component, a 32% to 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 5.6 cycles, which equated to a total drug cost of \$ [REDACTED] per patient.

Estimated PBS usage & financial implications

- 6.77 This resubmission was not considered by DUSC.
- 6.78 The resubmission, like the November 2016 submission, used an epidemiological approach to estimate the utilisation and financial impact of listing ibrutinib on the PBS for the treatment of relapsed or refractory mantle cell lymphoma.
- 6.79 Unlike the November 2016 submission, the resubmission estimated treatment duration of ibrutinib and R-CHOP using the progression free survival Kaplan-Meier curves from the economic model. As ibrutinib is taken until progression, the Kaplan-Meier curves were used to estimate the number of patients remaining on treatment each month and then, the estimated total number of treatment months. The average treatment duration in the resubmission was estimated to be 24.98 months. In the November 2016 submission it was estimated to be 23.4 months.

Table 15: Estimated use and financial implications of ibrutinib listing

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of ibrutinib use						
Patients initiating treatment	■	■	■	■	■	■
Months of ibrutinib treatment	■	■	■	■	■	■
Number of scripts dispensed ^a	■	■	■	■	■	■
Estimated financial implications of ibrutinib						
Cost to PBS/RPBS	■	■	■	■	■	■
Copayments	■	■	■	■	■	■
Cost to PBS/RPBS less copayments	■	■	■	■	■	■
Estimated financial implications for R-CHOP and pegfilgrastim						
Cost to PBS/RPBS	■	■	■	■	■	■
Copayments	■	■	■	■	■	■
Cost to PBS/RPBS less copayments	■	■	■	■	■	■
Estimated net cost to PBS/RPBS/MBS						
Net cost to PBS/RPBS	■	■	■	■	■	■
Net cost to MBS	■	■	■	■	■	■
Net cost to PBS/RPBS + MBS	■	■	■	■	■	■
November 2016 submission						
Net cost to PBS/RPBS	■	■	■	■	■	■
Net cost to MBS	■	■	■	■	■	■

Source: Calculated during the evaluation based on "Ibrutinib_RRMCL_Section_4.xlsx"

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RPBS = Repatriation Pharmaceutical Benefits Scheme

^a Based on the Kaplan-Meier estimators for progression free survival from the economic model (treatment months x 95.96% (dose intensity))

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be less than \$10 - \$20 million per year.

6.80 The resubmission estimated a net cost to PBS/RPBS and MBS of \$60 - \$100 million over the first six years. The net cost was lower than estimated in the November 2016 submission due to the lower ibrutinib drug costs, reduced patients numbers and the use of the Kaplan-Meier method to estimate treatment utilisation.

6.81 The PSCR (p4) argued that the number of prevalent mantle cell lymphoma patients estimated in the resubmission for 2017 (less than 10,000) was reasonable. The PSCR stated that the prevalent population estimated by the AIHW (less than 10,000) was for the year 2010 and therefore, extrapolation of this population to less than 10,000 in 2017 was required.

6.82 The PSCR (p4) argued that the number of patients eligible for ibrutinib should be higher than that for lenalidomide because the listing proposed is less restrictive and prevalent patients were appropriately included.

6.83 The evaluation considered there was potential for the net cost per year of listing ibrutinib to the PBS/RPBS to be greater or less than the estimate in the resubmission given that:

- there was uncertainty in the estimated number of treated patients as:
 - treatment duration of ibrutinib was model-based; and
 - the estimated rate of patients who relapse and receive second-line therapy (■%) could be higher or lower;
- the cost off-sets were uncertain as:
 - other immunochemotherapies, which could be used in place of R-CHOP, might have been more or less expensive;
 - treatment duration of R-CHOP was model-based; and
 - the treatment of adverse events with PBS medications could be greater as the submission only considered costs associated with neutropenia.

6.84 The ESC considered there were uncertainties related to the estimated proportion of patients who relapse and receive second-line therapy (■%) and the proportion of patients with WHO scores of two or less (■■■■%) and the uptake rate (■%).

6.85 The PBAC considered that the estimated number of treated patients and the associated financial costs were overestimated, this was in part due to assuming a high uptake rate and the same uptake for prevalent and incident patients. The PBAC further considered there was potential for leakage of ibrutinib outside the intended patient population, for example as use in the first-line setting in patients unable to tolerate R-CHOP.

Quality use of medicines

6.86 The resubmission did not provide specific information on the quality use of medicines.

Financial management – risk sharing arrangements

6.87 The resubmission stated that the sponsor would be open to exploring a Risk Share Agreement which would be of similar structure (and with a similar intent) to that of ibrutinib for relapsed or refractory chronic lymphocytic leukaemia.

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 mantle cell lymphoma on the basis of an unacceptably high incremental cost per quality adjusted years (QALY) gained. Further, the PBAC considered that the financial impact was high and likely overestimated.

7.2 The PBAC acknowledged the high clinical need for additional effective and well tolerated treatments for relapsed/refractory mantle cell lymphoma.

7.3 The PBAC considered that ibrutinib had superior efficacy compared with R-CHOP, however the magnitude of the benefit remained uncertain as it was based on a naïve indirect comparison that included retrospective analyses of heterogeneous patient

groups in the R-CHOP arm. In addition, the comparison was between trial and non-trial based patients; the trial-based temsirolimus patients might have been healthier and had a better prognosis. Despite the low quality of the evidence, the PBAC considered that ibrutinib was likely to offer benefit in an area of high clinical need.

- 7.4 The PBAC noted that updated safety data had been presented from the final analysis of the MCL-3001 trial of ibrutinib, and also that the resubmission had updated its safety claim since the previous submission. The PBAC considered that the updated claim, that ibrutinib was associated with superior comparative safety versus active treatment with R-CHOP, was reasonable.
- 7.5 The PBAC noted that the resubmission had presented scenario analyses to generate four ICERs. The PBAC considered that Scenarios 1 and 3 were overly optimistic as the overall survival curves did not converge within the model time horizon. Scenario 2 was considered uncertain, and likely optimistic, given it (along with Scenario 1) was based on adjusted trial results.
- 7.6 The PBAC noted that Scenario 4 was the most conservative of the scenarios presented, but considered that it still reflected optimistic assumptions given the uncertain magnitude of the incremental benefit, convergence to ten years and the utility differences between the treatment arms. However, overall, the PBAC considered that Scenario 4 had addressed many of its previous concerns.
- 7.7 The PBAC considered that the ICER/QALY resulting from Scenario 4 of the model, \$105,000/QALY - \$200,000/QALY gained, was unacceptably high. The PBAC considered that a significant price reduction would be required to bring the ICER/QALY into an acceptable range, particularly in the context of the uncertain incremental benefit of ibrutinib compared with R-CHOP.
- 7.8 With regard to the financial estimates, the PBAC considered that the patient numbers were significantly overestimated by the resubmission for the reasons outlined in paragraphs 6.83 and 6.85. The Committee acknowledged that uptake of ibrutinib was likely to be high, but that the uptake rate (■%) was overestimated in the resubmission.
- 7.9 The PBAC considered that any resubmission would need to provide a substantial price reduction for ibrutinib, to address the unacceptably high ICER/QALY and overall financial impact. The PBAC considered that patient numbers would need to be revised to lower estimates for a Risk Share Agreement to be useful.
- 7.10 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to

recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

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