

5.04 BENDAMUSTINE

**powder for injection, 100mg and 25mg (DPMA 200mg);
RIBOMUSTIN[®]; Janssen-Cilag Pty Ltd**

1 Purpose of Application

- 1.1 The submission sought section 100, Authority Required listing for bendamustine in combination with rituximab for the treatment of Stage III-IV indolent Non-Hodgkin's Lymphoma (iNHL) and Stage III-IV of Mantle Cell Lymphoma (MCL) in previously untreated patients, and bendamustine (monotherapy) for patients with rituximab-refractory Non-Hodgkin's Lymphoma (NHL).

2 Requested listing

- 2.1 The submission requested listing in three patient populations, as outlined below. Suggestions and additions proposed by the Secretariat to the requested listings are added in italics and suggested deletions are crossed out with strikethrough.

a. Induction for previously untreated indolent CD20 positive non-Hodgkin's lymphoma:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BENDAMUSTINE powder for injection 100 mg x 1 vial	200 mg	11	\$ [REDACTED] (public hospital)	Ribomustin Janssen-Cilag Pty Ltd
powder for injection 25 mg x 1 vial			\$ [REDACTED] (private hospital)	

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Category / Program	Section 100 (efficient funding of chemotherapy arrangements) public/private hospital
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:	Previously untreated
Severity:	Stage III or IV
Condition:	Indolent CD20 positive non-Hodgkin's lymphoma
Treatment phase:	Induction treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	The treatment must be in combination with rituximab, AND The condition must be previously untreated, AND <i>The condition must be symptomatic,</i> AND <i>The treatment must be for induction treatment purposes only,</i> AND <i>Patient must not receive more than 6 cycles (12 doses) of treatment under this restriction.</i>
Administrative Advice	<i>No increase in the maximum number of repeats may be authorised</i>

b. Induction for previously untreated mantle cell lymphoma:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BENDAMUSTINE powder for injection 100 mg x 1 vial powder for injection 25 mg x 1 vial	200 mg	11	\$ [REDACTED] (public hospital) \$ [REDACTED] (private hospital)	Ribomustin Janssen-Cilag Pty Ltd

Category / Program	Section 100 (efficient funding of chemotherapy arrangements) public/private hospital
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:	Previously untreated
Severity:	Stage III or IV
Condition:	CD20 positive mantle cell lymphoma
Treatment phase:	Induction treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined

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Clinical criteria:	The treatment must be in combination with rituximab, AND The condition must be previously untreated, AND <i>The condition must be symptomatic,</i> AND <i>The treatment must be for induction treatment purposes only,</i> AND Patient must not receive more than 6 cycles (12 doses) of treatment under this restriction AND The patient must not be eligible for stem cell transplantation.
Administrative Advice	<i>No increase in the maximum number of repeats may be authorised</i>

c. Treatment for rituximab-refractory indolent non-Hodgkin's lymphoma:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BENDAMUSTINE powder for injection 100 mg x 1 vial powder for injection 25 mg x 1 vial	275 mg	15	\$ [REDACTED] (public hospital) \$ [REDACTED] (private hospital)	Ribomustin Janssen-Cilag Pty Ltd

Category / Program	Section 100 (efficient funding of chemotherapy arrangements) public/private hospital
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
Severity:	Stage III or IV
Condition:	Indolent CD20 positive non-Hodgkin's lymphoma
Treatment phase:	<i>Re-induction treatment</i>
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	The treatment must be as monotherapy, AND The condition must be refractory to rituximab AND The patient must not receive more than 8 cycles (16 doses) of treatment under this restriction, AND <i>The patient must not have received previous treatment with this drug.</i>
Definitions	To be considered refractory to rituximab the patient must have had no response to a rituximab-containing treatment OR The patient must have had progression within 6 months of receiving a rituximab-containing treatment.

2.2 The basis for the requested listing was a cost-utility evaluation of bendamustine plus rituximab compared with R-CHOP (rituximab, cyclophosphamide, doxorubicin,

vincristine, prednisone) for the treatment of iNHL or MCL, in patients who have not received prior treatment. Listing was also requested for bendamustine monotherapy in rituximab-refractory iNHL, however no economic evaluation was presented for the use of bendamustine in this patient population.

3 Background

- 3.1 TGA status: Bendamustine was TGA registered on 30 June 2014 for the following indications:
- i) First-line treatment of chronic lymphocytic leukaemia (Binet stage B or C);
 - ii) Previously untreated indolent CD20-positive, stage III-IV Non-Hodgkin's Lymphoma, in combination with rituximab;
 - iii) Previously untreated indolent CD20-positive, stage III-IV Mantle Cell Lymphoma in combination with rituximab, in patients ineligible for autologous stem cell transplantation; and
 - iv) Relapsed/Refractory indolent Non-Hodgkin's Lymphoma.
- 3.2 Bendamustine is TGA-registered for use in previously untreated iNHL and MCL in combination with rituximab, and the clinical evidence for bendamustine in these indications is in combination with rituximab. However, rituximab is neither TGA approved nor PBS-listed for MCL, or for previously untreated sub types of iNHL other than follicular lymphoma. The Pre-Sub-Committee Response stated that bendamustine in combination with rituximab is TGA-registered for those indications, and therefore rituximab is TGA-registered for those indications when used in combination with bendamustine. However, the ESC noted that it was unclear how patients would access subsidised concomitant rituximab in these indications.
- 3.3 Bendamustine has not been considered by the PBAC before.

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

4 Clinical place for the proposed therapy

- 4.1 The submission proposed a change to the clinical management algorithm as follows: use of bendamustine plus rituximab as a first-line treatment in iNHL and MCL, and use of bendamustine monotherapy as a last-line treatment in patients with rituximab-refractory iNHL (in patients without previous exposure to bendamustine).

5 Comparator

- 5.1 In the previously untreated iNHL and MCL settings, the main comparator was R-CHOP, and the evaluator considered that this was appropriate.
- 5.2 In the rituximab-refractory iNHL setting, the comparator was best supportive care, and the evaluator considered that this was appropriate.

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

6 PBAC 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 (10), health care professionals (3) and organisations (2) via the Consumer Comments facility on the PBS website relating to bendamustine. The comments described a range of benefits of treatment with bendamustine including the potential for patients to lead a normal life during remission and the favourable adverse event profile noting that the adverse effects of R-CHOP can be debilitating.
- 6.3 Representatives of the PBAC met with Lymphoma Australia prior to the PBAC meeting, and reported the following key points to the PBAC in relation to the agenda items for CLL and indolent NHL:
 - Consumers place high importance on having access to the best available treatments. Where cure is not possible, the eventual goal would be to enable indolent lymphomas and CLL to be treated as chronic diseases. Ultimately patients may die of conditions unrelated to their lymphoma.
 - Patients may relapse multiple times in the course of the disease, and will be treated on relapse. As PBS subsidy may influence the choice of treatment, subsidising the most clinically effective treatments is critical to ensure the best value for the taxpayer.
 - Patients may be diagnosed at a young age and live for years after diagnosis, and therefore place a high value on PFS. Patients who are well during the progression free period can resume day-to day functions including participating in the workforce and family life. In this context, the decision for the patient rests on a balance of the PFS gained against the quality of life impacts of drug toxicity. The psychological impact of patients' fear of relapse can have a highly detrimental effect on their quality of life.

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- With regard to bendamustine, Lymphoma Australia noted that bendamustine has been available overseas for many years, but noted that this was the first application for PBAC consideration of the drug in Australia.

6.4 The PBAC noted and welcomed this input. PBAC recognises that a drug may be useful even when it does not provide a survival advantage, but does provide quality of life benefits. In terms of using PFS to value the benefits of a drug, PBAC recalled that some of the most informative submissions seen to date have presented economic models that incorporate the impacts on quality of life when patients are in a PFS state, capturing the fact that PFS is not a homogenous state. It was noted that exploring how patients could provide more input to rigorous measurement of Quality of Life would be valuable in future consumer submissions.

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

Clinical trials

6.5 For previously untreated iNHL and MCL patients: The submission was based on two head-to-head trials:

- the StiL trial (N=514) that compared bendamustine plus rituximab (B-R) to R-CHOP, and
- the BRIGHT trial (N=447) that compared B-R to either R-CHOP or R-CVP. This trial is on-going.

The data from StiL were used to inform the economic evaluation, while the data from BRIGHT were not used directly to inform the economic model, but were used as supportive evidence and in sensitivity analyses.

- For rituximab-refractory patients: The submission presented two small single-arm studies of bendamustine monotherapy in patients with rituximab-refractory iNHL: SDX-105-03 trial (N=100) and SDX-105-01 trial (N=76). No comparative evidence was provided. The ESC noted that there is currently an ongoing randomised, controlled trial in the rituximab-refractory iNHL patient population, with bendamustine intervention compared to treatment of physician's choice. The submission did not present an economic model for rituximab-refractory iNHL.

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

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Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Previously untreated iNHL and MCL		
Direct randomised trials		
StiL (NHL 1-2003) NCT00991211	Rummel et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. <i>Lancet</i> 381: 1203-10	Lancet 2013; 381: 1203-10
BRIGHT Study NCT008770065	Flinn et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study.	Blood (2014); 123 (19): 2944-2952
Non-randomised studies		
SDX-105-01 NCT00069758	Friedberg et al. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a phase II multicentre, single-agent study.	Journal of clinical oncology (2008); 26 (2):204-210
SDX-105-03 NCT00139841	Kahl et al. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin's lymphoma.	Cancer (2010); 116: 106-114

Source: Attachment B, of the commentary.

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

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
B-R vs R-CHOP/R-CVP in previously untreated iNHL and MCL						
StiL	549	OL, R Median PFS 69.5 mths in B-R, 31.2 mths in R-CHOP	Low	Treatment naïve, CD 20+, Stage III-IV iNHL and MCL patients	PFS, OS (5 years)	Used
BRIGHT	447	OL, R ORR of 97% in B-R, 91% in R-CHOP	Low	Treatment naïve	Response rate, CR, PR	Used for sensitivity analyses

DB=double blind; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; CR = complete response; PR = partial response; R=randomised.

Source: compiled during the evaluation

6.8 The ESC noted that the StiL trial was designed to demonstrate non-inferiority and therefore a per protocol analysis was used. Intention-to-treat results were not available because the submission relied on published data.

6.9 The BRIGHT study reported aggregated results for the comparator arm for the efficacy outcomes (i.e. R-CHOP and R-CVP were combined), but disaggregated data for safety outcomes because the safety profile of R-CHOP is distinct from that of R-CVP.

Comparative effectiveness- previously untreated iNHL and MCL patients

6.10 For previously untreated iNHL and MCL patients:
 - based on the StiL trial, B-R was associated with a longer median progression free survival (PFS) compared to R-CHOP. The PFS result was statistically significant.

- based on the BRIGHT trial, B-R was associated with a higher overall response rate (ORR) compared to R-CHOP/R-CVP.
- 6.11 The StiL trial presented results by histological sub-group and reported that:
- for follicular lymphoma, the HR for PFS was 0.61 (95% CI: 0.42, 0.87).
 - for MCL, median PFS was increased by 13.3 months (B-R arm 35.4 months compared with 22.1 months in R-CHOP arm), with a HR for PFS of 0.49 (95% CI 0.28, 0.79).
- 6.12 The BRIGHT trial found that CR rate for B-R (31%) was non-inferior to that for R-CHOP/R-CVP (25%). Although the CR rate for B-R was greater than the 22% threshold for non-inferiority set up in the trial, it was not statistically superior to the R-CHOP/R-CVP arm ($p=0.1269$).

Comparative harms - previously untreated iNHL and MCL patients

- 6.13 Previously untreated iNHL and MCL patients:
- based on the StiL trial, B-R was associated with a lower incidence of grade 3 and 4 haematological adverse events (except for lymphocytopenia, where 31% more cases were reported in the B-R group) and alopecia, paresthesia and stomatitis compared to R-CHOP.
 - based on the BRIGHT trial, B-R was also associated with a lower incidence of non-haematological adverse events, such as alopecia, paresthesia and mucosal inflammation, compared to R-CHOP.
- 6.14 There were some adverse events for which the rate was higher with B-R compared with R-CHOP:
- Based on the StiL trial, B-R was associated with an increased risk of skin reactions compared with R-CHOP (16% and 9% of patients experienced erythema in the B-R and R-CHOP arms, respectively).
 - Based on the BRIGHT trial B-R was associated with a higher incidence of vomiting compared with R-CHOP (29% versus 13%, Relative Risk of 2.20 [95% CI: 1.22, 3.96]), while the StiL trial reported a similar incidence of vomiting in both treatment groups (B-R = 46%, R CHOP = 42%).

Benefits/harms - previously untreated iNHL and MCL patients

- 6.15 The summary of the comparative benefits and harms for B-R versus R-CHOP was updated by the ESC and is presented in the table below.

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Summary of comparative benefits and harms for Bendamustine- Rituximab and R-CHOP

Benefits						
Progression Free Survival						
StiL	B-R	R-CHOP	Absolute Difference	HR (95% CI)		
Progressed (events)	103/261	143/253	-	0.58 (0.44, 0.74)		
Median (mths)	69.5 (26.1, -)	31.2 (15.2, 65.7)	38.3			
Complete Response						
Trial	B-R	R-CHOP**	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				B-R	R-CHOP**	
StiL	104/261	76/253	1.326 (1.05, 1.69)	39.8	30	0.10 (0.05, 0.18)
BRIGHT	67/213	52/206	1.246 (0.92, 1.69)	31.5	25.2	0.06 (-0.02, 0.15)
Harms						
	B-R	R-CHOP	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				B-R	R-CHOP	
Neutropenia (Grade 3-4 haematological event)						
StiL	77/261	173/253	0.43 (0.35, 0.53)	29.5	68.4	-0.39 (-0.47, -0.31)
BRIGHT	40/103	85/98	0.45 (0.35, 0.58)	38.8	87.7	-0.48 (-0.59, -0.36)
Neuropathy/Paresthesia (non-haematological event, all grades)						
StiL	18/261	73/253	0.24 (0.15, 0.39)	6.9	28.9	-0.22 (-0.28, -0.16)
BRIGHT	9/103	43/98	0.20 (0.10, 0.39)	8.7	43.9	-0.35 (-0.46, -0.24)
Infection/infectious episodes (non-haematological event, all grades)						
StiL	96/261	127/253	0.73 (0.60, 0.90)	36.8	50.2	-0.13 (-0.22, -0.05)
BRIGHT	57/103	56/98	0.97 (0.76, 1.24)	55.3	57.1	-0.02 (-0.16, 0.12)

StiL trial median duration of follow-up is 45 months; BRIGHT study follow-up is up to 8 cycles (B-R arm 1 cycle length is 28 days; R-CHOP or R-CVP arms 1 cycle length is 21 days), median follow-up is Not Reported (data is not mature, as per the planned 5 years minimum follow-up by the trial design)

**BRIGHT study presents aggregate data for R-CHOP/R-CVP benefits outcome, and disaggregated data (R-CHOP only) for safety outcomes (Note: the safety profile of R-CHOP is distinct from that of R-CVP)

Abbreviations: B-R=bendamustine-rituximab; C=Cyclophosphamide; H=Doxorubicin; O (in R-CHOP) / V (in R-CVP) =Vincristine; P=Prednisone; R=Rituximab D = risk difference; RR = risk ratio; CR= complete response; PFS=progression-free survival

Source: Compiled during the evaluation, Tables B.6.1, B.6.2 and B.6.3, of the commentary

- 6.16 On the basis of head-to-head StiL trial, the comparison of B-R and R-CHOP resulted in:
- An improvement in median PFS of approximately 38 months (StiL trial)
- 6.17 On the basis of head-to-head trials presented in the submission, for every 100 patients treated with B-R in comparison to R-CHOP (StiL trial) or R-CHOP/R-CVP (BRIGHT study) resulted in:
- Approximately 10 additional patients would have a complete response (StiL trial)
 - Approximately 6 additional patients would have complete response (BRIGHT study)

- 6.18 On the basis of head-to-head trial presented in the submission, for every 100 patients treated with B-R in comparison to R-CHOP there would be:
- Approximately 39 to 48 fewer cases of grade 3-4 neutropenia based on the StiL and BRIGHT trials respectively
 - Approximately 22 to 35 fewer cases of neuropathy based on the StiL and BRIGHT trials respectively
 - Approximately 2 to 13 fewer cases of infectious episodes based on the BRIGHT and StiL trials respectively

Clinical claim

- 6.19 Previously untreated iNHL and MCL patients:
The submission claimed that bendamustine plus rituximab is superior in terms of both effectiveness and safety when compared to R-CHOP for the first-line treatment of iNHL and MCL. The evaluation considered that this claim was adequately supported for the outcome of PFS, based on the StiL trial data; however no overall survival benefit was demonstrated. At the time of analysis (median follow up of 45 months), median overall survival was not reached in either group.
- 6.20 The StiL trial did not include rituximab maintenance treatment, which reduced the applicability of the trial to the Australian setting and may have led to an underestimate of PFS in both arms of the trial. The impact on the relative efficacy of B-R compared to R-CHOP is unknown, but it is possible that the exclusion of rituximab maintenance may have overestimated the comparative PFS advantage of B-R.
- 6.21 Rituximab refractory patients (Bendamustine monotherapy):
The submission made no comparative clinical or safety claim for bendamustine monotherapy in rituximab refractory patients.

Economic analysis

- 6.22 Rituximab-refractory iNHL: An economic evaluation for the rituximab-refractory iNHL population was not included in the submission, as no relevant randomised controlled trials or comparative clinical trials were identified. The ESC considered that the submission had not presented any evidence upon which to draw conclusions as to the comparative effectiveness, safety and cost-effectiveness of bendamustine in this setting. Thus, the ESC noted that there was no evidence upon which to determine the risk-benefit profile of bendamustine in this setting and considered that there is an opportunity cost associated with using resources that do not produce any benefit. Therefore, the ESC considered that the submission's lack of any comparative information in this setting was unreasonable.
- 6.23 Previously untreated iNHL and MCL: The submission presented a stepped-economic evaluation, based on the StiL trial that compared the costs and consequences of treatment with B-R versus R-CHOP in the first-line treatment of patients with iNHL or MCL.

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Summary of model structure and rationale

Component	Summary
Time horizon	20 years in the model base case versus 7.72 years in the trial
Outcomes	LYG, QALYs
Methods used to generate results	Cohort expected value analysis
Health states	3 state Markov model: progression-free, progressed disease and death
Cycle length	4 weekly cycles (half-cycle correction applied)
Transition probabilities	Transition probabilities were based on KM curves from recreated individual patient data. For 20 year model a Weibull extrapolation to the trial data beyond the time horizon of the study was used.

Source: compiled during the evaluation

- 6.24 The key influences on the ICER were the utility values for the progression-free and progressed disease state, time horizon and body surface area (BSA) used in calculating the average dose per patient.

Key drivers of the model

Description	Method/Value	Impact
Utility values	Increase in utility difference between PFS and PD state	HIGH, favours B-R
Progression to death	Lower hazard rate from progression-free state to death compared with progressed disease state.	Moderate, favours B-R
Time horizon	20 years (base case) 10 years; assumed from 60 month trial duration	Moderate, favours B-R Moderate, favours R-CHOP
KM estimates (LCB)	Use of lower confidence bound of KM estimates and extrapolation for B-R and R-CHOP	Moderate, favours R-CHOP
KM estimates (UCB)	Use of upper confidence bound of KM estimates and extrapolation for B-R and R-CHOP	Moderate, favours B-R
BSA (1.59 kg/m ²)	Use of lower BSA to estimate average dose per patient	Moderate (favours B-R)
BSA (2.01 kg/m ²)	Use of lower BSA to estimate average dose per patient	Moderate (favours R-CHOP)

Source: compiled during the evaluation

PFS = progression-free survival, PD = progressed disease; LCB = Lower confidence bound; UCB = upper confidence bound; KM = Kaplan-Meier; BSA = body surface area. B-R = Bendamustine + rituximab; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

- 6.25 The table below summarises the results of the stepped economic analysis.

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Results of the stepped economic evaluation

Step and component	B-R	R-CHOP	Increment
Step 1: median trial follow-up results (45 months)			
Costs	\$ ██████████	\$ ██████████	\$ ██████████
PFS years	██████████	██████████	██████████
QALYs	██████████	██████████	██████████
Incremental cost/PFS years			\$ ██████████
Incremental cost/QALY			\$ ██████████
Step 2: trial based results (7.72 years)			
Costs	\$ ██████████	\$ ██████████	\$ ██████████
PFS years	██████████	██████████	██████████
QALYs	██████████	██████████	██████████
Incremental cost/PFS years			\$ ██████████
Incremental cost/QALY			\$ ██████████
Step 3: modelled evaluation (extrapolation of PFS estimates 20 years)			
Costs	\$ ██████████	\$ ██████████	\$ ██████████
PFS years	██████████	██████████	██████████
QALYs	██████████	██████████	██████████
Incremental cost/PFS years			\$ ██████████
Incremental cost/QALY			\$ ██████████

Source: Table D.4/D.5/D.6, pp206-209, Section D of the submission

- 6.26 The table below summarises the results of the sensitivity analyses presented in the submission and the commentary, and additional sensitivity analyses requested by the ESC.

Sensitivity analyses

Description	Method/Value	ICER
Progression to death	Lower hazard rate from progression-free state to death compared with progressed disease state.	\$15,000/QALY - \$45,000/QALY
Time horizon	10 years 30 years	\$45,000/QALY - \$75,000/QALY \$15,000/QALY - \$45,000/QALY
KM estimates (LCB)	Lower bound of Confidence Interval Upper bound of Confidence Interval	\$45,000/QALY - \$75,000/QALY \$15,000/QALY - \$45,000/QALY
Body Surface Area	1.59 kg/m ² 2.01 kg/m ²	\$15,000/QALY - \$45,000/QALY \$15,000/QALY - \$45,000/QALY
Utility values	PFS = 0.780, PDS = 0.618	\$15,000/QALY - \$45,000/QALY
The utilities used in the model were:	PFS = 0.840, PDS = 0.618*	\$15,000/QALY - \$45,000/QALY
	PFS = 0.770, PDS = 0.618*	\$15,000/QALY - \$45,000/QALY
0.805 for Progression-free:	PFS = 0.805, PDS = 0.728*	\$75,000/QALY - \$105,000/QALY
0.618 for Progressed Disease	PFS = 0.805, PDS = 0.508*	\$15,000/QALY - \$45,000/QALY
	PFS = 0.805, PDS = 0.736**	\$75,000/QALY - \$105,000/QALY

Source: compiled during the evaluation

Abbreviations: PFS=progression-free state, PD=progressed disease state

*Based on confidence intervals around the base case utility, calculated from the standard errors in Wild et al (2006)

**Utility values sourced from Dewilde et al (2014)

- 6.27 The resulting ICER was \$15,000/QALY - \$45,000/QALY. The ICER was highly sensitive to the time horizon and the proportion of patients in the progression-free and the progressed disease states as well as the utility values applied to these states. The submission presented univariate and multivariate analyses. A sensitivity analysis conducted during the evaluation demonstrated that as the utility values of the progression-free state and progressed disease state converged, the ICER significantly increased.

- 6.28 The ESC noted that the ICER is sensitive to the incremental difference in utilities between the ‘progression-free’ health state and the ‘progressed disease’ health states. The ESC noted the sensitivity analyses that use utility values based on confidence intervals around the base case utility, calculated from the standard errors in Wild et al (2006) and utility values sourced from Dewilde et al (2014).
- 6.29 The ESC noted that the model structure does not include subsequent therapies, such as rituximab maintenance and the multiple lines of subsequent rituximab-based regimens. This does not reflect treatment patterns in clinical practice and underestimates future costs. The ESC agreed with the PSCR that the exclusion of subsequent lines of therapy may favour R-CHOP given the higher rate of subsequent salvage therapy observed in the R-CHOP arm compared to the B-R arm. However, the ESC considered that a more reliable model structure would need to appropriately reflect the possibility of additional lines of treatment, with their costs and health benefits.
- 6.30 The ESC noted that the costs and benefits were not linked within the model over time, and that this limited the usefulness of the model and any sensitivity analyses.
- 6.31 The PBAC noted that the source of the utility values used in the economic model was a poster presentation (Wild et al 2006). The PBAC noted that the pre-progression and post-progression utilities in Figure 2 of Wild et al were mislabelled. Wild et al grouped patients with follicular lymphoma into 5 disease states (newly diagnosed, active disease relapsed, partial response, remission-full response, and disease-free). Wild et al stated that this was “following a literature review and discussion with clinical experts”, and that these 5 health states “correspond to the health state categorisation commonly employed in clinical trials of the condition”. In order for the utilities to fit a particular cost effectiveness model, Wild et al also grouped the categories to form two broader health states, which were described as the “macro health states” of pre-progression and post-progression. The model structure for bendamustine used these two macro health states (‘progression free’ and ‘progressed disease’), informed by the Wild et al utilities.

Mantle Cell Lymphoma

- 6.32 A single economic evaluation was presented for both iNHL and MCL. The ESC considered that combining the two disease states in a single model would not be appropriate if there are substantial differences between the two conditions. The ESC considered that this may limit the potential usefulness of the model.
- 6.33 The submission attempted to account for this in sensitivity analyses by adjusting the hazard ratio to account for different proportions of patients with MCL. However, the ESC considered that this did not adequately account for other differences in disease characteristics between iNHL and MCL. The ESC noted that MCL has a median overall survival of between 5 and 7 years.¹ Therefore a shorter time horizon was tested in a univariate sensitivity analysis, for indicative purposes.

¹ <http://www.ils.org/content/nationalcontent/resourcecenter/freeeducationmaterials/lymphoma/pdf/mantlecelllymphoma.pdf>

Sensitivity analyses of shorter time horizons that more accurately reflect Mantle Cell Lymphoma

Time Horizon	ICER/QALY
5 years	\$75,000/QALY - \$105,000/QALY
7 years	\$45,000/QALY – \$75,000/QALY

Source: compiled at the request of the ESC. The median progression-free period for patients with MCL is 20 months and the median overall survival is between 5 and 7 years.¹

- 6.34 The ESC noted that other structural, methodological and content issues may need to be taken into account in order to accurately assess the cost-effectiveness of B-R in MCL. For example, other inputs into the model are based on the pooled data for all the NHL subtypes that were enrolled in the StiL trial. In particular, the model transition probabilities are based on pooled Kaplan-Meier estimates of PFS. The ESC noted that if the PFS for the MCL sub-group could be used, the cost-effectiveness may improve, even with the shorter time horizons.
- 6.35 The Pre-PBAC response stated that this approach was biased against B-R because it did not capture all the consequences of treatment with bendamustine.

Drug cost/patient/course/year: \$ [REDACTED] (iNHL/MCL), \$ [REDACTED] (monotherapy).

- 6.36 For previously untreated iNHL and MCL: The total cost per patient per course was estimated to be \$ [REDACTED] for B-R, \$ [REDACTED] for R-CHOP and \$ [REDACTED] for R-CVP. These costs were based on an average BSA of 1.8 kg/m² and an average number of cycles of 5.58, 5.63 and 6 for B-R, R-CHOP and R-CVP respectively.
- 6.37 Rituximab-refractory iNHL: The total cost per patient is \$ [REDACTED] based on bendamustine monotherapy for an average of 6 cycles.

Estimated PBS usage & financial implications

- 6.38 The submission used an epidemiological incidence approach to estimate the utilisation and financial implications associated with the requested PBS listing of bendamustine.
- 6.39 The submission was considered by the DUSC. The main issues identified by the DUSC in relation to the previously untreated iNHL and MCL indications were:
- DUSC considered that a prevalence approach would have been preferable to the incidence approach taken particularly in year 1 of listing. DUSC was convinced that there would be a prevalent pool of patients awaiting treatment, due to the chronic and relapsing-remitting nature of the disease. The patient numbers were therefore likely to be underestimated.
 - DUSC considered the linear incidence projections were not appropriate for all of the disease subtypes, particularly in relation to MCL, Waldenstrom's macroglobulinaemia and small lymphocytic leukaemia.
 - DUSC expected that patients may cycle through all of the available treatments, such that bendamustine would delay rather than substitute R-CHOP or R-CVP. Therefore the DUSC considered that attributing market share proportions of the

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eligible population was not appropriate, when all eligible patients may try bendamustine;

- Rituximab maintenance was not included;
- There is potential for bendamustine to be used outside the requested restriction; including treatment as a second line and subsequent lines of therapy, use in rituximab-refractory MCL patients and leakage to CLL patients; and
- Wastage of vials was not considered.

6.40 The submission estimated use and financial implications for the previously untreated indications are outlined below.

Estimated use and financial implications (iNHL and MCL) first line

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated					
Market share	%	%	%	%	%
Scripts ^a					
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
Net cost to MBS	\$	\$	\$	\$	\$
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$	\$	\$	\$	\$

^a Included services for both bendamustine and rituximab

Source: Table 9, p8, Executive Summary of the Commentary; Table E30/E34/E35, p258/p264/p265, Section E of the submission

6.41 The redacted table above shows the estimated use and financial implications of bendamustine to the PBS, RPBS and MBS for the first-line treatment of iNHL and MCL is less than \$10 million in the first year and \$10 - \$20 million in subsequent years.

6.42 The main issues identified by the DUSC in relation to the rituximab-refractory iNHL population were:

- The prevalent population is more likely to be the initial patient group; and
- The timing of the patients in the estimates (where last line treatment occurs the year after diagnosis) was not representative of the disease progression.

Estimated use and financial implications (Rituximab-refractory)

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated					
Market share	%	%	%	%	%
Scripts ^a					
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
Net cost to MBS	\$	\$	\$	\$	\$
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$	\$	\$	\$	\$

^a Included services for both bendamustine and rituximab

Source: Table 10, p8, Executive Summary of the Commentary

- 6.43 The redacted table above shows that the estimated use and financial implications of bendamustine to the PBS, RPBS, and MBS for the treatment of rituximab-refractory iNHL is less than \$10 million per year in each of the first five years of listing.

7 PBAC Outcome

- 7.1 The PBAC deferred its decision on bendamustine in previously untreated iNHL and MCL noting: that the economic model submitted by the sponsor did not provide a reliable estimate of the cost-effectiveness of bendamustine; the pending trial data (BRIGHT); and also the high price compared to other brands of bendamustine imported under the TGA Special Access Scheme. The PBAC did not recommend bendamustine in the rituximab-refractory patient population.
- 7.2 The PBAC agreed that R-CHOP was the appropriate comparator in the iNHL and MCL patient populations, and that best supportive care was the appropriate comparator in the rituximab-refractory patient population.
- 7.3 The PBAC welcomed the input received from individuals and organisations in support of the submission for bendamustine, including at the consumer hearing. The comments outlined a range of benefits of bendamustine therapy including improved quality of life and a more favourable adverse event profile than currently available therapies.
- 7.4 The submission had requested PBS listing in three patient populations:
- i. Previously untreated indolent CD20-positive, stage III-IV NHL, in combination with rituximab.
 - ii. Previously untreated indolent CD20-positive, stage III-IV Mantle Cell Lymphoma in combination with rituximab, in patients ineligible for autologous stem cell transplantation; and
 - iii. Refractory indolent Non-Hodgkin's Lymphoma
- 7.5 Bendamustine is also TGA registered for the first line treatment of chronic lymphocytic leukaemia, and the PBAC considered this to be an area of high clinical need. However, the sponsor did not submit an application to the PBAC for this indication.
- 7.6 For MCL, the PBAC considered that the bendamustine restriction should specify that

use is for patients who are not eligible for stem cell transplant, which is consistent with the StiL trial inclusion criteria.

- 7.7 The PBAC considered the comparative safety and effectiveness data in each of the three requested patient populations groups.

Indolent Non-Hodgkin's Lymphoma

- 7.8 For the first-line treatment of iNHL, the PBAC considered that the claim of superior comparative effectiveness of B-R compared to R-CHOP was adequately supported by the data for the outcome of PFS based on the StiL trial data. In particular, the PBAC considered that this claim was well supported for the sub-group of patients with follicular lymphoma. Fifty-three percent of patients enrolled in the StiL trial had follicular lymphoma, and the HR for PFS in this sub-group was 0.61 (95% CI: 0.42, 0.87).
- 7.9 The committee noted that no overall survival benefit was demonstrated in the StiL trial, but that median overall survival was not reached in either group at the time of analysis (median follow up of 45 months). The economic model did not incorporate any differences in overall survival between B-R and R CHOP, and the PBAC considered that this was appropriate.
- 7.10 The BRIGHT trial reported that B-R was non-inferior, but not statistically significantly superior, to R-CHOP/R-CVP for the outcome of Complete Response (CR) rates (CR rates of 31% and 25% respectively; p=0.1269). Follow-up of the BRIGHT trial is ongoing for PFS and OS, which were secondary outcomes. The trial protocol pre-specified that a 5-year minimum follow-up time was required to evaluate these outcomes, and the estimated trial completion date listed on clinicaltrials.gov is March 2017. The PBAC considered that this follow-up data may provide further information as to the magnitude of the incremental effect of B-R over R-CHOP.
- 7.11 For the first-line treatment of iNHL and for MCL, the PBAC considered that bendamustine plus rituximab was superior to R-CHOP in terms of comparative safety, but noted that bendamustine is not without adverse events.

Mantle Cell Lymphoma

- 7.12 For the first-line treatment of MCL, the PBAC considered that the claim of superior effectiveness of B-R compared to R-CHOP was adequately supported for the outcome of PFS, based on the StiL trial data.

Rituximab-refractory iNHL

- 7.13 For patients with rituximab-refractory iNHL, the PBAC agreed with the ESC that there was a lack of comparative information, and it was not possible to draw any conclusions regarding the comparative effectiveness, safety and cost-effectiveness of bendamustine in this setting.

Economic Model

- 7.14 The PBAC considered that the two “macro health states” of pre-progression and post-progression from Wild et al were not an appropriate basis for the economic evaluation. The five disease states outlined in Wild et al (newly diagnosed, active disease relapsed, partial response, remission-full response, and disease-free) and their corresponding utility values more accurately reflect the course of the condition.
- 7.15 The PBAC noted the issues with the economic model raised by the ESC (refer to Paragraphs 6.28-6.36), and considered that an appropriate model would:
- Incorporate a structure that appropriately reflects the different levels of disease progression using the five disease state utilities from Wild et al, rather than the two macro health state utilities.
 - Incorporate the impact of further lines of treatment with their costs and health benefits;
 - Provide separate economic evaluations for indolent NHL and MCL;
 - Use a 10 year time horizon for the economic evaluation for MCL, with a 7 year time horizon used in a sensitivity analysis; and
 - Justify the use of a 20 year time horizon for indolent NHL.
- 7.16 In light of these issues, the PBAC considered that the submitted model did not provide a reliable basis for estimating the cost-effectiveness of bendamustine. Therefore, the PBAC requested that, for the previously untreated iNHL and MCL patient populations, the sponsor either:
- Provide a major re-submission that addresses the issues in the model as outlined in Paragraph 7.15. However, the PBAC noted that this may require individual patient level data, to which the sponsor may not have access.
 - propose an entry price that mitigates the risk that the model does not accurately estimate the true cost-effectiveness of bendamustine. In forming this view, the PBAC noted: the safety advantage over R-CHOP; the requested economic evaluation may not be possible because of limitations on data available to the sponsor; and the high asking price compared to other brands of bendamustine imported under the TGA Special Access Scheme. In the absence of a reliable economic evaluation, the PBAC requested that the Department review the listing of bendamustine once longer term follow-up data from the BRIGHT trial are available, to ensure that the PFS data from the BRIGHT trial are consistent with the data presented in this submission from the STiL trial. Should there be substantially less incremental improvement over R-CHOP in PFS (hazard ratio, median) observed in the BRIGHT study compared to the STiL trial, the sponsor would need to provide a reliable economic evaluation to support continued listing of the product at the listed price.

Financial estimates

- 7.17 The STiL trial did not include subsequent rituximab maintenance treatment. Both rituximab maintenance and B-R prolong PFS and no evidence was provided to demonstrate that these benefits would be additive. Therefore the PBAC considered that the use of rituximab maintenance should not be permitted following induction with B-R. This would require a flow-on change to the PBS restrictions for rituximab in

the maintenance setting.

- 7.18 Therefore, the PBAC considered that the financial estimates should account for the exclusion of rituximab maintenance therapy following treatment with bendamustine.

Registration of concomitant rituximab

- 7.19 The PBAC noted the need for patients to have subsidised access to concomitant rituximab.

Outcome:

Deferred

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

The Sponsor is disappointed with the outcome and does not agree with the rationale for the PBAC's recommendation. The sponsor is, however, working to resolve the issues raised by the PBAC, so that patients can access this important medicine in a timely manner. A re-submission will be considered at the July 2015 meeting.