

4.03 BENDAMUSTINE, powder for injection 100 mg vial, 1 powder for injection 25 mg vial, 1, Ribomustin[®], Jansen-Cilag Pty Ltd

1 Purpose of Application

- 1.1 The minor re-submission sought a section 100 Authority Required Efficient Funding of Chemotherapy (EFC) Streamlined listing of 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.

2 Requested listing

- 2.1 The re-submission requested listing for first line iNHL and first line MCL. The re-submission did not seek listing of bendamustine for rituximab refractory iNHL.
- 2.2 The re-submission requested a streamlined restriction, consistent with arrangements for the Section 100 EFC Programme. All suggested changes proposed in the re-submission that differ from the outcome of the PBAC March 2015 meeting are represented with strikethrough:

First-line indolent non-Hodgkin's lymphoma

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
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)		

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 type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required – Electronic <input checked="" type="checkbox"/> Streamlined

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

First-line mantle cell lymphoma

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
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)		

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 type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required – Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	The treatment must be in combination with rituximab, AND The condition must be previously untreated, AND The condition must be symptomatic, 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	No increase in the maximum number of repeats may be authorized

- 2.3 The clinical criteria were amended to exclude “induction treatment purpose only” due to the PBAC recommendation that rituximab maintenance therapy is not to be permitted following induction with bendamustine-rituximab (B-R) (paragraph 7.17, March 2015 PSD, bendamustine).
- 2.4 The PBAC had considered that the bendamustine restriction for MCL should specify that use is for patients who are not eligible for stem cell transplant, which is consistent with the StiL trial inclusion criteria (paragraph 7.6, March 2015 PSD, bendamustine).
- 2.5 The re-submission did not discuss the potential for leakage outside the PBS restriction including use as a second line and subsequent lines of therapy, as well as potential leakage to chronic lymphocytic leukaemia (CLL) patients. The PBAC had considered CLL to be an area of high clinical need. However, the sponsor did not submit an application to the PBAC for this indication (paragraph 7.5, March 2015 PSD, bendamustine).

For more detail on PBAC’s view, see section 7 “PBAC outcome”

3 Background

- 3.1 Bendamustine was TGA registered on 30 June 2014 for treatment of 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. The PBAC had noted the need for patients to have subsidised access to concomitant rituximab (paragraph 7.19, March 2015 PSD, bendamustine).
- 3.3 Bendamustine was previously considered by PBAC in March 2015 as a Major submission. The PBAC deferred its decision on whether to recommend bendamustine in previously untreated iNHL and MCL. The PBAC did not recommend bendamustine in the rituximab-refractory patient population (paragraph 7.1, March 2015 PSD, bendamustine).
- 3.4 The re-submission did not address the rejection of the previous requested listing for rituximab-refractory iNHL nor did it request a PBS listing in this patient group. The PBAC noted 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 rituximab-refractory iNHL (paragraph 7.13, March 2015 PSD, bendamustine).

3.5 The re-submission responded to the PBAC’s deferral of a decision to list bendamustine on the PBS for the treatment of first-line iNHL and MCL at the March 2015 PBAC meeting. Table 1 provides a summary of the key differences between the March 2015 submission and the re-submission, including PBAC comments on the March 2015 submission.

Table 1. Key differences between the March 2015 submission and the July 2015 minor submission

	March 2015 submission	July 2015 re-submission
Requested PBS listing for:	<p>First line indolent NHL, First line MCL, Rituximab-refractory indolent NHL</p> <p>PBAC comment (5.04 March 2015 PSD, bendamustine, paragraph 7.1): “The PBAC deferred its decision on bendamustine in previously untreated iNHL and MCL. The PBAC did not recommend bendamustine in the rituximab-refractory patient population.” The PBAC noted 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 the rituximab-refractory patient population” (5.04 March 2015 PSD, bendamustine, paragraph 7.13)</p>	<p>First line indolent NHL, First line MCL</p>
Requested restriction	<p>Restriction level/method: Authority required (In writing, telephone, emergency , electronic); and Streamlined</p>	<p>Restriction level/method: Streamlined</p>
Clinical evidence	<p>StiL trial (main evidence), median follow up 45 months: <u>Time to next treatment: HR 0.58 [95% CI 0.44, 0.74] p<0.0001</u>); <u>Salvage treatment: B-R arm (n74 patients), R-CHOP arm (n=116 patients);</u> OS at 5 years: complete response (CR) (all patients): 90.3%; partial response (PR) (all patients): 77.5% p=0.0008. CR (B-R patients): 91.0%; PR (B-R patients): 80.1% p=0.0044. CR (R-CHOP patients): 89.6%; PR (R-CHOP patients): 75.4% p=0.0737</p> <p>BRIGHT study (supportive evidence)</p>	<p>StiL trial (update December 2014), median follow-up 87 months: <u>Time to next treatment: HR 0.53, 95% CI: 0.40, 0.68, p<0.001</u>); <u>Salvage treatment: B-R arm (n=93 (36%) patients), R-CHOP arm (n=140 (55%)) with cross over into B-R treatment (n=69 out of 140 patients);</u> OS: 10-year survival rates iNHL HR 0.70 (0.48; 1.04) p=0.076; MCL HR 1.28 (0.69; 2.39) p=0.429.</p>
Economic evaluation	<p>Rituximab maintenance therapy not included in the economic model. iNHL and MCL patients combined Time horizon: 20 years 3 state Markov model</p>	<p>The re-submission addressed but did not provide:</p> <ul style="list-style-type: none"> - The separate economic evaluation for iNHL and MCL patients; - The time horizon for iNHL

	March 2015 submission	July 2015 re-submission
	<p>PBAC comment (paragraph 7.15, March 2015 PSD, bendamustine):</p> <p>“- 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.</p> <ul style="list-style-type: none"> - 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” . 	<p>patients;</p> <ul style="list-style-type: none"> - The 5 disease state model; - The impact of subsequent therapies. <p>The re-submission presented a sensitivity analysis which included rituximab maintenance in the R-CHOP patients.</p>
Financial estimates	<p>Rituximab maintenance therapy not included in the economic model.</p> <p>Net cost for Government Health budget over 5 years was \$60 – 100 million (excluding rituximab refractory patients, excluding rituximab maintenance in R-CHOP arm)</p> <p>PBAC comment (paragraph 7.18, March 2015 PSD, bendamustine): “...the PBAC considered that the financial estimates should account for the exclusion of rituximab maintenance therapy following treatment with bendamustine.”</p>	<p>Sensitivity analysis: R-CHOP + rituximab maintenance.</p> <p>Net cost <u>saving</u> for Government Health budgets over 5 years was under \$10 million (excluding rituximab refractory patients, including rituximab maintenance in R-CHOP arm)</p>
PBAC decision	Deferred	

Abbreviations: HR = hazard ratio, B-R = bendamustine+ rituximab, R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone.

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.

5 Comparator

- 5.1 The previous major submission considered by the PBAC in March 2015 nominated R-CHOP as the comparator. The PBAC had considered the nominated comparator to be appropriate in the iNHL and MCL patient populations (paragraph 7.2, March 2015 PSD, bendamustine). The nomination of R-CHOP (rituximab, cyclophosphamide,

doxorubicin, vincristine and prednisolone) as the comparator in the minor submission remained unchanged.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (2), health care professionals (2) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with bendamustine, including improved quality of life and survival, in addition to a reduction in adverse events compared with alternative, more toxic, treatments.

Clinical trials

6.3 No new clinical trials were presented in the re-submission. However, updated data from the previously presented StiL trial was presented. There was no update from the BRIGHT study.

6.4 The minor submission presented the following clinical trials:

Table 2. Trials and associated reports presented in the re-submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
StiL	Rummel et al. Bendamustine Plus Rituximab (B-R) Versus CHOP Plus Rituximab (CHOP-R) As First-Line Treatment in Patients with Indolent and Mantle Cell Lymphomas (MCL) – 7 Year Updated Results from the StiL NHL1 Study.	2014. 56th ASH Annual Meeting and Exposition. Abst 4407

Source: the minor re-submission

Comparative effectiveness

6.5 The resubmission presented an update of the StiL trial outcomes: median time to next treatment and proportion of patients treated with salvage treatment in both arms B-R and R-CHOP; 10-year survival data were also presented.

6.6 In the R-CHOP arm 49% of the patients who received salvage treatment received B-R. This showed switching/cross-over within the trial, and demonstrated the potential for leakage of B-R being into second-line therapy in practice.

6.7 The updated HR for the time to next treatment was 0.53 (95% CI: 0.40; 0.68, $p < 0.001$) compared with 0.58 (95% CI 0.44, 0.74, $p < 0.000$) presented in the March 2015 submission. Results were not reported by histological subtype of the disease.

6.8 The resubmission presented updated overall survival (OS) data; the results between the treatment arms were not statically significant. There was no difference in OS between the subgroups.

6.9 Table 3 summarises the updated results of StiL trial.

Table 3. Updated results for StiL trial

	Salvage treatment all, n(%)	Salvage treatment with B-R, n(%)	Time to next treatment HR (CI 95%)
Time to Next treatment			
B-R (N=261)	93 (36%)	NA	0.53 (0.40; 0.68), p<0.001
R-CHOP (N=253)	140 (55%)	69 (49% of 140 patients receiving salvage)	
OS	Deaths	10-year survival rate	HR
All lymphomas			
B-R (N=261)	65 (25%)	67.4%	0.70 (0.48; 1.04) p=0.076
R-CHOP (N=253)	76 (30%)	60.1%	
Excluding MCL patients			
B-R (N=215)	43 (20%)	71.9%	-
R-CHOP (N=205)	58 (28.3%)	61.5%	-
MCL patients (N=95)	-	-	1.28 (0.69; 2.39) p=0.429

Source: compiled from p11, of the re-submission. Notes: NSA = not applicable; B-R = bendamustine – rituximab; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

Comparative harms

6.10 The PBAC had considered that for the first-line treatment of iNHL and for MCL, bendamustine plus rituximab was superior to R-CHOP in terms of comparative safety, but had noted that bendamustine is not without adverse events (paragraph 7.11, March 2015 PSD, bendamustine).

Clinical claim

6.11 The March 2015 submission claimed that bendamustine plus rituximab was superior in terms of effectiveness and safety compared with R-CHOP for the first-line treatment of iNHL and MCL in patients who meet certain criteria. The re-submission did not seek to change the clinical claim presented in the original submission and accepted by PBAC. The PBAC had considered that the claim of superior comparative effectiveness of B-R compared to R-CHOP was adequately supported for the outcome of progression free survival (PFS), based on the StiL trial data for the first-line treatment of iNHL and MCL. The PBAC had also considered that B-R was superior to R-CHOP in terms of comparative safety, but noted that bendamustine is not without adverse events (paragraphs 7.8, 7.11 and 7.12, March 2015 PSD, bendamustine).

Economic analysis

6.12 In March 2015 the PBAC deferred its decision on bendamustine in previously untreated iNHL and MCL noting:

- the pending trial data (BRIGHT);
- the economic model submitted by the sponsor did not provide reliable estimate of the cost-effectiveness of bendamustine; and

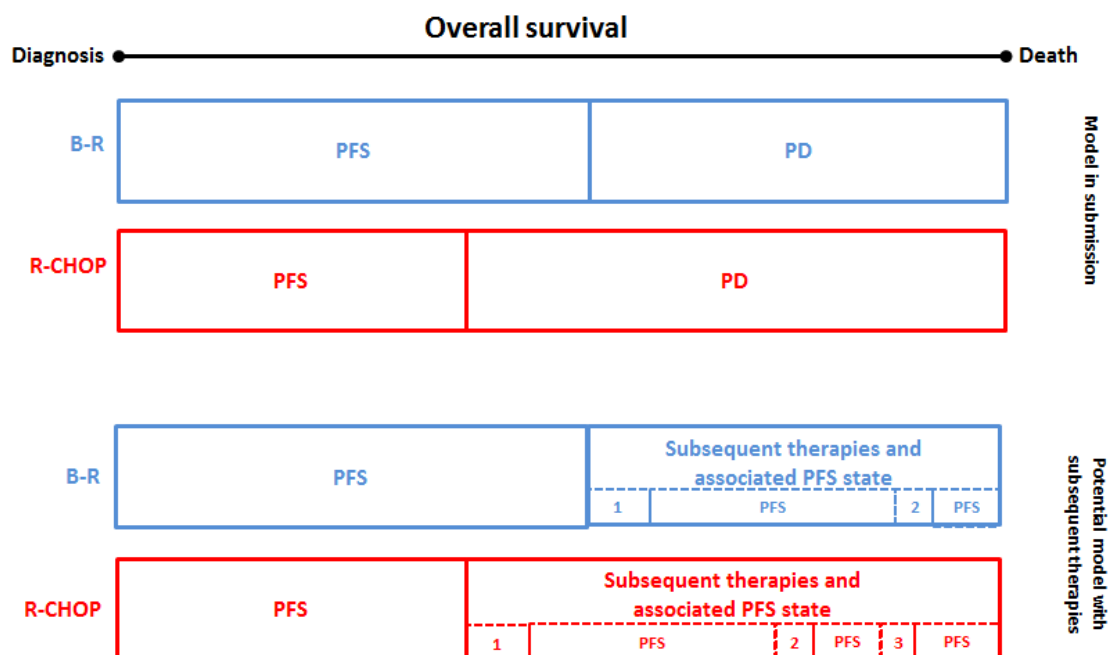
- the high price compared to other brands of bendamustine imported under the TGA Special Access Scheme.
- 6.13 The PBAC had requested that the listing of bendamustine to be reviewed by the Department upon the availability of longer term follow-up data from the BRIGHT study, to ensure that the PFS data from the BRIGHT trial are consistent with the data presented from the StiL trial. The PBAC had noted that 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 (paragraph 7.16, March 2015 PSD, bendamustine).
- 6.14 The minor resubmission stated that the suggestion by PBAC to use the BRIGHT study to confirm the cost-effectiveness of bendamustine post-listing was inappropriate, because:
- The BRIGHT study was used as supportive evidence for short term endpoints such as complete response and safety;
 - The sponsor was not aware of the date of release of BRIGHT study publication; although according to the ClinicalTrials.gov trial registry, the results for PFS and OS at the end of follow-up are anticipated to be reported in July 2017¹;
 - The BRIGHT study was not powered to detect differences in PFS and would not have long term follow-up data, resulting in higher uncertainty in the estimates of PFS and OS; and
 - The comparator of the BRIGHT study was R-CHOP (N=104) and R-CVP (N=119), which reduced the sample size in the R-CHOP arm.
- 6.15 The previous major submission, considered by PBAC in March 2015, presented a cost-utility analysis against R-CHOP, based on a Markov model with three disease states (progression-free, progressed disease and dead). The PBAC had considered that model submitted in March 2015 did not provide a reliable basis for estimating the cost-effectiveness of bendamustine and requested that a more appropriate model would include five disease states (diagnosed, active disease relapsed, partial response to therapy, remission/full response to therapy and disease-free) and their corresponding utility values (paragraph 7.14, March 2015 PSD, bendamustine).
- 6.16 The re-submission did not alter the economic model structure from the March 2015 submission. The re-submission stated that due to lack of access to patient level data the 5-disease state model was not possible. The re-submission stated that according to Wild et al (2006) it was reasonable to pool the 5-disease state utilities into two 'macro disease states'. The re-submission claimed that grouping three (partial response to therapy, remission/full response to therapy, disease-free) of the five utility states into one utility state (pre-progression) for the economic model was appropriate.
- 6.17 The PBAC had also considered that an economic model should incorporate the impact of further lines of treatment with their costs and health benefits (paragraph

¹ [clinicaltrials.gov website for BRIGHT study, bendamustine, NCT00877006](http://clinicaltrials.gov/ct2/show/study/NCT00877006). Accessed: 28 May 2015.

7.15, March 2015 PSD, bendamustine). The re-submission stated that the exclusion of further therapies in the economic analysis is a conservative approach as it favours R-CHOP.

- 6.18 The re-submission claimed that patients in the R-CHOP arm (according to the StiL trial results) would be more likely to receive subsequent therapies faster than patients in the B-R arm. The re-submission presented a graphical illustration to support its statement. See Figure 1 below.

Figure 1. Illustration of the impact that subsequent therapies have on health outcomes



Source: the re-submission

- 6.19 The resubmission claimed that (based on the figure above), R-CHOP patients were likely to experience more lines of subsequent therapies than B-R patients, and therefore the cost of subsequent therapies will be greater in R-CHOP patients than in B-R patients. Furthermore, the updated StiL trial data indicated that there was cross over in the R-CHOP arm and 49% received B-R as salvage treatment. The potential of B-R being administered after R-CHOP may need to be incorporated with the subsequent lines of treatment.
- 6.20 The re-submission presented a sensitivity analysis of the economic model by including rituximab maintenance for the responding follicular lymphoma patients who were treated with R-CHOP (applied to subgroup of follicular lymphoma patients who achieved a partial or complete response after treatment with R-CHOP). The assumption was that these R-CHOP patients would all receive rituximab maintenance therapy. The re-submission claimed that this was an extreme assumption.
- The re-submission adjusted the efficacy and cost values in the economic model;

- The re-submission noted the existing PRIMA trial (N=1217) (Salles et al 2010) evidence comparing (R-CHOP vs R-CVP vs R-FCM) + rituximab maintenance (versus observation) in first-line treatment of follicular lymphoma patients, resulting in the PFS HR of 0.55 (95% CI 0.44, 0.68, p<0.0001);
 - The HR of 0.55 was applied to the product of the proportion of follicular lymphoma patients in the StiL trial (54.3%) and the proportion of patients achieving CR or PR (91.3%). The resulting probability was applied to the Kaplan-Meier PFS estimates for R-CHOP (StiL trial) to estimate the proportion of patients whose hazard of progression was reduced due to rituximab maintenance;
 - The result of including rituximab maintenance therapy to the R-CHOP arm for the treatment of follicular lymphoma patients, indicated that the outcomes of R-CHOP + rituximab maintenance were not superior to B-R arm; and
 - the cost of R-CHOP + rituximab maintenance exceeded the cost of B-R alone.
- 6.21 The submission claimed that B-R dominated R-CHOP+ rituximab maintenance even without taking into account the costs of managing potential adverse events that might arise from rituximab maintenance therapy.
- 6.22 This assumption of rituximab maintenance in R-CHOP did not consider subsequent lines of therapy of the B-R arm which could receive R-CHOP as a second line therapy and other rituximab based therapies. The economic model presented in the resubmission was a simplification of the subsequent lines of therapy (in the sensitivity analysis). The PBAC had considered it appropriate to incorporate the impact of further lines of treatment with their costs and health benefits in the economic model (paragraph 7.15, 2015 PSD, bendamustine).
- 6.23 The PBAC had considered that a separate economic evaluation for iNHL and MCL was more appropriate (paragraph 7.15, March 2015 PSD, bendamustine). The minor re-submission disagreed with the PBAC, viewing such a model unnecessary, based on the following factors:
- the limitation of the available data (aggregated results published from StiL trial);
 - the re-submission analysed the difference between the subgroups based on the overall cohort that was recruited;
 - the HR for MCL was 0.49 (95% CI: 0.28, 0.79, p=0.0044), while HR for whole cohort was 0.58 (95% CI: 0.44, 0.74, 0<0.0001). The re-submission reiterated that 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 (paragraph 6.34, March 2015 PSD, bendamustine);
 - the proportion of MCL patients in trial compared to expected PBS population was 18.3% and ██████%, respectively; and
 - a sensitivity analysis was presented in the major submission, where HR was adjusted in the overall cohort, which resulted in an increase of ICER by less than \$15,000.
- 6.24 The PBAC had considered that for the economic evaluation of MCL a 10-year time horizon was more appropriate, and a 7-year time horizon was to be tested in the

sensitivity analysis (paragraph 7.15, March 2015 PSD, bendamustine). The PBAC noted that MCL had a median OS between 5 and 7 years (paragraph 6.33, March 2015 PSD, bendamustine). The minor re-submission did not directly address this issue.

- 6.25 The PBAC had also noted that an appropriate economic model should justify the use of a 20 year time horizon for iNHL (paragraph 7.15, March 2015 PSD, bendamustine). The minor re-submission provided evidence from the AIHW report, “Cancer in Australia, An Overview, 2014” which presented a 20 year relative survival data for NHL patients (all forms of NHL). The data demonstrated that 50% of the cohort was alive at 20 years post diagnosis.
- 6.26 The minor re-submission noted that at 8 years approximately 40% of B-R patients had not progressed compared to 20% of R-CHOP patients.
- 6.27 The minor re-submission stated that the ICER was unchanged from the previous submission (\$15,000 - \$45,000/QALY). However, due to updates in the co-payment and prices of doxorubicin, the new ICER is \$15,000 - \$45,000/QALY.
- 6.28 The PBAC had noted that addressing the issues in the model may require patient level data and that the sponsor may not have access to such data (paragraph 7.16, March 2015 PSD, bendamustine). In regards to a proposed entry price, the minor re-submission did not propose a new price of bendamustine.
- 6.29 Based on the issues with the economic model, the PBAC had requested that for the previously untreated iNHL and MCL patient populations, the sponsor either:
- Provide a major resubmission that addressed the issues in the models; OR
 - Propose an entry price that mitigates the risk that the model does not accurately estimate the true cost-effectiveness of bendamustine.
- (paragraph 7.16, March 2015 PSD, bendamustine).
- 6.30 The minor re-submission provided the following arguments as to why a new entry price was not proposed:
- Bendamustine (Ribomustin) is the only brand of bendamustine which is listed on the ARTG and the sponsor was not involved in the supply of bendamustine in Australia under any other price;
 - Several changes to the economic model (subsequent therapies, rituximab maintenance) would improve the ICER in favour of bendamustine; while other changes (5-state disease model, separate economic evaluations for indolent NHL and MCL) would not have a major impact on the ICER;
 - The comparative effectiveness, safety and cost-effectiveness of bendamustine was demonstrated through the incremental analysis, with a resulting ICER of B-R over R-CHOP of \$15,000 - \$45,000/QALY; and
 - All sensitivity analyses resulted in ICERs in the range of \$15,000 - \$45,000/QALY to \$45,000 - \$75,000/QALY. This range of ICERs represents the sensitivity analyses presented the major submission and current re-submission; however, the sensitivity analysis conducted by the evaluator and presented in the Commentary to the major submission for progressed disease state demonstrated that ICER varied between \$15,000 - \$45,000/QALY to

\$75,000 - \$105,000/QALY (paragraph 6.26, March 2015 PSD, bendamustine).

Estimated PBS usage & financial implications

- 6.31 The PBAC had considered that the financial estimates should account for the exclusion of rituximab maintenance therapy following treatment with bendamustine (paragraph 7.18, March 2015 PSD, bendamustine).
- 6.32 The re-submission presented a sensitivity analysis of the financial estimates by including rituximab maintenance therapy following the first-line treatment of responding follicular lymphoma patients who were treated with R-CHOP.
- The re-submission reported an estimated net cost-saving to government health budgets of less than \$10 million over 5 years if rituximab maintenance were included only in the R-CHOP arm.
- 6.33 The re-submission also revised the financial estimates with updated PBS and MBS costs where relevant (reduced and a change in patient co-payment as of January 2015). The revised estimates have minor differences to the base case presented in the previous submission.
- 6.34 At the July 2015 meeting the PBAC recommended that tiered financial caps should apply in order to limit the risk of use of bendamustine outside the recommended restriction. The PBAC considered that the first level of caps should be based on the patient numbers provided in the major submission for bendamustine (March 2015), with a rebate to apply above that cap to [REDACTED]. The PBAC considered that if patient numbers substantially exceeded the estimates, it would most likely be driven by utilisation outside of the restriction e.g. in patients with CLL. The PBAC therefore recommended that if utilisation exceeded [REDACTED]% above the cap, a [REDACTED]% rebate should be implemented.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of bendamustine for the treatment of indolent non-Hodgkins Lymphoma and Mantle Cell Lymphoma.
- 7.2 The PBAC considered that bendamustine presented a less toxic alternative to existing treatments for NHL and MCL and accepted that it improved progression free survival.
- 7.3 The PBAC noted that the end of follow-up results for PFS and OS from the BRIGHT trial were anticipated to be reported in July 2017 and reiterated that it would wish to see and review these data when released.
- 7.4 The PBAC noted the submission's arguments as to why the economic model should incorporate the impact of further lines of treatment with their cost and health benefits,

however restated its strong preference in general to include subsequent therapies to enable robust assessments of cost-effectiveness in diseases such as iNHL.

- 7.5 The PBAC noted the sensitivity analyses presented by the re-submission and considered that they provided some assurance that BR will not be inferior to R-CHOP followed by rituximab maintenance in patients with follicular lymphoma.
- 7.6 The PBAC noted the submission's arguments as to why separate economic evaluations for iNHL and MCL would be unnecessary, and considered that they were acceptable. The PBAC also considered that while the trial was underpowered to detect important differences in overall survival in the MCL subgroup, the data overall were supportive of a benefit in this small subgroup of patients with high and unmet clinical need.
- 7.7 The PBAC noted the submission's argument that the lack of access to patient level data prevented the use of the 5-disease state model, however rejected the conclusions of Wild et al that it was reasonable to pool the 5-disease state utilities into two 'macro disease states'. The PBAC considered that such pooling creates additional uncertainty, and is highly undesirable for use in applications for indolent lymphomas and like diseases, such as iNHL and CLL. The PBAC also noted the AIHW report "Cancer in Australia, An Overview, 2014" and considered that these data, while not conclusive, did support the sponsor's contention that a 20 year time horizon would be appropriate for iNHL. The PBAC noted that implicit in accepting a prolonged time horizon is the responsibility for the model to take into account all important health states and additional therapies, wherever possible. The PBAC noted the inherent disconnect between using both a three-state health model and a 20 year time horizon.
- 7.8 The PBAC noted analyses performed in the minor submission exploring the financial impact of no use of rituximab maintenance after induction therapy with bendamustine plus rituximab. Such maintenance is commonly used after R-CHOP induction for patients with follicular lymphoma, but is not part of the bendamustine plus rituximab regimen. The PBAC noted that the analysis included the extreme assumption that all patients on R-CHOP would receive subsequent rituximab maintenance therapy. Therefore the projected cost savings of less than \$10 million over 5 years were considered the upper limit of what may occur if bendamustine was to be PBS-listed. Nevertheless, the PBAC did consider that there would be reduced expenditure on rituximab maintenance and that listing of bendamustine on the PBS for first line therapy of iNHL and mantle cell lymphoma could reasonably be expected to result in cost savings to the Commonwealth. While the PBAC remained concerned about the limitations of the 3-state health model and the application of a 20-year time horizon in the context of this disease, these concerns were diminished given projections that the listing of bendamustine could be cost saving to the Commonwealth. In this context, the PBAC considered that the re-submission's ICER of \$15,000 - \$45,000/QALY was a reasonable representation of the cost-effectiveness of bendamustine.
- 7.9 The PBAC considered, however, that these cost savings would not be realised in practice if maintenance therapy with rituximab was used following BR induction therapy, noting that the cost-effectiveness of this approach had not been established.

The PBAC recalled its advice from March 2015 that the use of rituximab maintenance should not be permitted following induction with bendamustine, and that this would require a flow-on change to the PBS restrictions for rituximab in the maintenance setting. The PBAC thus recommended that the clinical criterion “The treatment must be for induction purposes only” should remain in the requested restriction for bendamustine, and that the current maintenance listing for rituximab be amended to include an additional clinical criterion that precludes maintenance following bendamustine plus rituximab induction.

- 7.10 Advice to the Minister under subsection 101(3BA) of the National Health Act 1953
In accordance with subsection 101(3BA) of the National Health Act 1953, the PBAC advised that it is of the opinion that, on the basis of the material available to it, bendamustine should not be treated as interchangeable on an individual patient basis with any other drugs(s) or medicinal preparation(s).
- 7.11 The PBAC considered that bendamustine was not suitable for prescribing by nurse practitioners.
- 7.12 The PBAC considered that the 20 Day Rule should not apply, noting that Section 100 EFC listings require dispensing of a PBS supply per treatment dose and that dispensing may be required at shorter than 20 day intervals.
- 7.13 The PBAC considered that no increase to the maximum quantities or repeats should be authorised.
- 7.14 The PBAC also noted that the submission did not address the use of bendamustine in CLL, and considered that a future submission for CLL would address the concerns regarding utilisation outside the restriction requested in the current restriction.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

First-line indolent non-Hodgkin's lymphoma

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
bendamustine powder for injection 100 mg x 1 vial powder for injection 25 mg x 1 vial	200 mg	11	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:	Indolent CD20 positive non-Hodgkin's lymphoma			
Treatment phase:	Induction treatment			
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined			
Clinical criteria:	The treatment must be in combination with rituximab, AND The condition must be previously untreated, AND The condition must be symptomatic, AND The treatment must be for induction treatment purposes only, AND Patient must not receive more than 6 cycles (12 doses) of treatment under this restriction.			
Administrative Advice	No increase in the maximum number of repeats may be authorised			

First-line mantle cell lymphoma

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
bendamustine powder for injection 100 mg x 1 vial powder for injection 25 mg x 1 vial	200 mg	11	Ribomustin	Janssen-Cilag Pty Ltd

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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:	CD20 positive mantle cell lymphoma
Treatment phase:	Induction treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	The treatment must be in combination with rituximab, AND The condition must be previously untreated, AND The condition must be symptomatic, 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	No increase in the maximum number of repeats may be authorized

9 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.

10 Sponsor's Comment

Janssen is pleased the PBAC recognised that bendamustine in combination with rituximab is superior to R-CHOP in terms of comparative efficacy and safety. Additionally the PBAC recognised that listing bendamustine on the PBS could reasonably be expected to result in cost savings to the Commonwealth.

Janssen has no issue in principle with risk-sharing arrangements as a mechanism to share and manage uncertainty. However, the proposed arrangement places the burden of risk of use outside the intended population

entirely on the Sponsor. Further, it places cost containment measures on the Sponsor for use that is greater than forecast but still within the intended population.

Janssen is currently working through the issues with the Department of Health.