Bendamustine for the treatment of lymphoma: 24 month predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

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Abstract

Purpose

To compare the predicted and actual utilisation of bendamustine for the treatment of lymphoma in the first 24 months of Pharmaceutical Benefits Scheme (PBS) listing.

Restriction (abridged)

Previously untreated stage III or IV indolent CD20 positive non-Hodgkin's lymphoma (iNHL)
Treatment Phase: Induction treatment
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

Previously untreated stage III or IV CD20 positive mantle cell lymphoma (MCL)
The same clinical criteria as above plus;
- Patient must not be eligible for stem cell transplantation.

Data Source

The analyses use data from the Department of Human Services (DHS) prescriptions database from January 2002 to the end of September 2018 and the DHS Authority approvals database from May 2016 (date of listing of bendamustine) to the end of September 2018.

Key Findings

- The number of patients commencing treatment with bendamustine was similar to predicted in Year 1 and [redacted]% more than predicted in Year 2.
- The number of prescriptions supplied was [redacted]% less than expected in Year 1 and similar to predicted in Year 2. The lower than expected number of prescriptions per patient per year can, in part, be explained by patients initiating toward the end of one listing year and completing their induction regimen in the following year.
- There was some use of bendamustine outside the restriction:
  - 10.5% of patients had more than 6 cycles (12 prescriptions) of bendamustine.
  - at least 5.4% of patients treated with bendamustine had prior chemotherapy regimens indicative of treatment for iNHL or MCL;
  - 4.5% of patients may be being treated for chronic lymphocytic leukaemia (CLL).
- 23% of patients receiving bendamustine had more than 6 rituximab prescriptions suggesting rituximab maintenance therapy after bendamustine + rituximab (B-R) induction.

Purpose of analysis

To compare the predicted and actual utilisation of bendamustine for the treatment of lymphoma in the first 24 months of Pharmaceutical Benefits Scheme (PBS) listing.

Background

Bendamustine was PBS listed on 1 May 2016 for previously untreated stage III or IV indolent CD20 positive non-Hodgkin's lymphoma (iNHL) and mantle cell lymphoma (MCL).

Non-Hodgkin's lymphoma (NHL) is a general term for cancers that develop in the lymphatic tissue. Lymphomas arise when developing B- and T-cell lymphocytes undergo a malignant change and multiply in an uncontrolled way, escaping normal immune recognition.

Lymphomas are staged according to the Ann Arbor staging system. Stage III and IV lymphomas are defined as having spread throughout the lymphoid system and involve disease on both sides of the diaphragm (stage III) or extralymphatic tissues (stage IV).

Approximately 95% of B-cell lymphomas express the CD20 antigen[1]. The CD20 antigen is specific to B-cells and not expressed by T-cells.

The iNHL group includes follicular lymphoma (FL), marginal zone lymphoma (MZL), small lymphocytic lymphoma (SLL), lymphoplasmacytic lymphoma (LPL) and Waldenström's macroglobulinaemia (WM).

Pharmacology[2]

Bendamustine hydrochloride is an alkylating antitumour agent with unique activity. The antineoplastic and cytocidal effect of bendamustine hydrochloride is based essentially on a cross-linking of DNA single and double strands by alkylation. As a result, DNA matrix functions and DNA synthesis and repair are impaired. Bendamustine is active against both quiescent and dividing cells.

The active substance revealed no or very low cross-resistance in human tumour cell lines with different resistance mechanisms.

The exact mechanism of action of bendamustine remains unknown.

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[1] Therapy of B-Cell Lymphoma with Anti-CD20 Antibodies Can Result in the Loss of CD20 Antigen Expression Thomas A. Davis, Debra K. Czerwinski and Ronald Levy, Clin Cancer Res March 1 1999 (5) (3) 611-615;
[2] Ribomustini® (bendamustine hydrochloride), Australian Approved Product Information, Janssen-Cilag Pty Ltd, 1-5 Khartoum Road, Macquarie Park NSW 2113, updated 22 June 2018. Accessed on: 23 October 2018 at: https://www.tga.gov.au/product-information-0

Therapeutic Goods Administration (TGA) approved indications[2]

Bendamustine was TGA registered on 30 June 2014 for the treatment of the following conditions:

- First-line treatment of chronic lymphocytic leukaemia (Binet stage B or C).
- Previously untreated indolent CD20-positive, stage III-IV Non-Hodgkin's lymphoma, in combination with rituximab.
- Previously untreated CD20-positive, stage III-IV Mantle Cell Lymphoma in combination with rituximab, in patients ineligible for autologous stem cell transplantation.
- Relapsed/Refractory indolent Non-Hodgkin's lymphoma.

Dosage and administration[2]

Combination therapy with rituximab for first-line non-Hodgkin's lymphoma and mantle cell lymphoma; 90 mg/m^2 on days 1 and 2 of a 4-week cycle for up to 6 cycles.

Treatment may be interrupted, delayed or terminated or dose may be reduced in the case of toxicity. See the Product Information for more details.

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from the TGA (Product Information) and the TGA (Consumer Medicines Information).

PBS listing details (as at October 2018)

Date of listing on PBS

The 25 mg and 100 mg injection vials were PBS listed on 1 May 2016. The PBS item codes are shown in Table 1.

Table 1: PBS Efficient Funding of Chemotherapy listing of bendamustine (1 October 2018)

Item	Name, form & strength, pack size	Max. Amount	Rpts	Setting	DPMA	Brand name and manufacturer
10760L	bendamustine hydrochloride 100 mg injection, 1 vial bendamustine hydrochloride 25 mg injection, 1 vial	200 mg	11	Public Hospital	$1699.08	Ribomustin® Janssen-Cilag Pty Ltd
10763L	bendamustine hydrochloride 100 mg injection, 1 vial bendamustine hydrochloride 25 mg injection, 1 vial	200 mg	11	Private Hospital	$1760.90	

Source: the PBS website.

Restriction from 1 May 2016 to 30 September 2018[3]

The below restrictions apply to both PBS items.

Authority required (STREAMLINED): 6075
Previously untreated stage III or IV indolent CD20 positive non-Hodgkin's lymphoma
Treatment Phase: Induction treatment
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.

Authority required (STREAMLINED): 6124
Previously untreated stage III or IV CD20 positive mantle cell lymphoma
Treatment Phase: Induction treatment
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, AND
- Patient must not be eligible for stem cell transplantation.

Current PBS listing details are available from the PBS website.

Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

Original submission, March 2015 PBAC

The first submission for bendamustine, considered at the March 2015 PBAC meeting, requested listing for the treatment of lymphoma in three patient populations:

1. Induction for previously untreated indolent CD20 positive non-Hodgkin's lymphoma.
2. Induction for previously untreated mantle cell lymphoma.
3. Treatment for rituximab-refractory indolent non-Hodgkin's lymphoma

[3] From 1 October 2018, the bendamustine listing was extended to allow reinduction treatment for follicular lymphoma patients refractory to treatment with rituximab, and to include previously untreated Stage II "bulky" iNHL patients. These changes were made in the context of the listing of obinutuzumab and did not impact the utilisation data in the report which are up to the end of September 2018.

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 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.

The PBAC agreed that R-CHOP[4] 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.

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.

Bendamustine was 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.

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 was consistent with the Study group indolent Lymphomas (StiL) trial inclusion criteria.

The StiL trial did not include subsequent rituximab maintenance treatment. Both rituximab maintenance and bendamustine plus rituximab (B-R) prolong progression free survival (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.

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

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

The submission was considered by 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 considered 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.

[4] Drugs in the R-CHOP combination include rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate and prednisone.

- 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 eligible population was not appropriate, when all eligible patients may try bendamustine;
- Rituximab maintenance was not included;
- There was 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.

For further details refer to the Public Summary Document from the March 2015 PBAC meeting.

Minor resubmission, July 2015 PBAC

A subsequent minor resubmission, considered at the July 2015 PBAC meeting, requested listing for first line iNHL and MCL, but did not seek listing for rituximab refractory iNHL.

The PBAC recommended the listing. The PBAC considered that bendamustine presented a less toxic alternative to existing treatments for NHL and MCL and accepted that it improved PFS. 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;
- 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 was commonly used after R-CHOP induction for patients with follicular lymphoma, but is not part of the bendamustine plus rituximab regimen. 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. The PBAC considered, however, that these cost savings would not be realised in practice if maintenance therapy with rituximab was used following B-R 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; and

- 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.

The PBAC considered that no increase to the maximum quantities or repeats should be authorised.

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 further details refer to the Public Summary Document from the July 2015 PBAC meeting.

Approach taken to estimate utilisation

The minor resubmission to the July 2015 PBAC used an epidemiological incidence approach to estimate the number of patients eligible for bendamustine. This followed the same approach and assumptions as the original submission to the March 2015 PBAC.

Table 2 shows the parameters used to estimate utilisation and financial impact and is sourced from the original submission to March 2015 PBAC. The incidence of iNHL and MCL was based on data requested from the AIHW Australian Cancer Database (ACD) from 1982 to 2009/10. These data were then projected to the estimate years of 2015 to 2020. The proportion of patients with Stage III/IV, CD20 positive disease and market share were based on published literature and market research.

Table 2: Key parameters used to estimate utilisation and financial impact

Data	Value	Source
Estimating patient numbers		
Incidence data (crude, age and sex-specific) for iNHL subtypes (FL, MZL, SLL, LPL and WM) and MCL in Australia from 1982 through to 2009/10	Various	Requested from the AIHW Australian Cancer Database (ACD)
Proportion of FL patients with stage III/IV disease	67%	Armitage 1998 and Nabhan 2012
Proportion of iNHL (exc FL) patients with stage III/IV disease	62%	Armitage 1998 (weighted average)
Proportion of MCL patients with stage III/IV disease	80%	Armitage 1998, Abrahamsson 2014 and Leux 2014
Proportion of iNHL (inc FL) and MCL patients who are CD20 positive	95%	Davis 1999
Proportion of MCL patients who are ineligible for ASCT	63%	Calculated from transplant data obtained from the ABMTR
Proportion of iNHL (inc FL) patients who are treated	100%	Assumption
Proportion of MCL patients who are treated	100%	Dreyling 2014 and Martin 2009
Market share estimates of R-CHOP and R-CVP in iNHL (inc FL) if bendamustine is not PBS listed	[redacted]	Market research; re-calculated relative proportion based on R-CHOP and R-CVP equalling 100% of the market.
Proportion of patients who switch to B-R coming from R-CHOP each year if bendamustine is listed for iNHL	[redacted]	Assumption; assumed to be the same as the current market share split of R-CHOP and R-CVP.
Proportion of patients switching from R-CVP to B-R each year if bendamustine is listed for iNHL	[redacted]	
Market share estimates of B-R, R-CHOP and R-CVP in iNHL (inc FL) if bendamustine is PBS listed	[redacted]	Sponsor commissioned market research.

	[redacted]	
Market share estimates of R-CHOP in MCL if bendamustine is not PBS listed	[redacted]	Market research shows R-CHOP to be the most common treatment for MCL and is assumed to represent the entire market.
Market share estimates of B-R and R-CHOP in MCL if bendamustine is PBS listed	[redacted]	Sponsor commissioned market research.
Estimating costs of the chemotherapies		
Average number of cycles of B-R	5.58	StiL trial
Average number of cycles of R-CHOP	5.63	StiL trial
Average number of cycles of R-CVP	6	EviQ.org.au and BRIGHT trial
Average patient BSA (m^2), SD	1.8 (±0.21)	Dooley 2004
Proportion of prescriptions supplied in a private hospital	66%	pbs.gov.au
Proportion of prescriptions supplied in a public hospital	34%	pbs.gov.au

[a] Average number of cycles was not reported.
iNHL=indolent non-Hodgkins lymphoma; FL=follicular lymphoma; MCL=mantle cell lymphoma; CD20=cluster of differentiation 20; ASCT=autologous/allogeneic stem cell transplant; B=bendamustine; C=cyclophosphamide; H=doxorubicin; P=prednisone; R=rituximab; O (in R-CHOP)/V (in R-CVP)=vincristine; BSA=body surface area; ABMTR=Australia Bone Marrow Transplant Registry

Methods

PBS prescription data for bendamustine dispensed from 1 May 2016 (date of listing on the PBS) to 30 September 2018 were extracted from the DHS PBS prescription database.[5] PBS prescription data were used to determine the number of prescriptions supplied and the number of incident and prevalent patients.

Indication for a prescription was based on the Streamline Authority code. If this was not a valid value then the restriction code in the DHS Authority Approval database was used. A small proportion of patients (3.3%) had a dispensing history of bendamustine for both iNHL and MCL, likely due to prescribing or dispensing coding error. In these cases, a patient's most common valid indication was used in the analyses. There were a small number of patients (0.6%) supplied bendamustine prescriptions without a valid code. These patients were excluded from analyses by indication, but included in total patient and prescription counts in Table 3.

[5] The date of processing of a PBS prescription may differ from the date of dispensing. Consequently there may be differences in data reported by date of dispensing or processing (such as that available publicly available from DHS Medicare website).

Managing small cell sizes in tables and figures

Where the patient or prescription count is between 1 and 5 (inclusive), a figure data point is set to 5 and a table cell is set to "<=5" to protect patient confidentiality.

Dose distribution

Under the Efficient Funding of Chemotherapy (EFC) program, a prescription corresponds to a single infusion. The prescribed dose for the infusion is recorded on the PBS prescription record. The dose analysis used bendamustine prescriptions from 1 May 2016 (date of listing on the PBS) to 30 September 2018.

Medicine initiation sequence analysis

This analysis was used to assess whether bendamustine is being used outside of the PBS restriction for previously treated iNHL or MCL or for non-subsidised indications, specifically CLL. For all patients that have initiated bendamustine, prescription data for selected medicines was extracted from the DHS PBS prescription database. The medicines were rituximab, prednisolone, cyclophosphamide, vincristine, doxorubicin, chlorambucil, fludarabine, ibrutinib, ofatumumab and obinutuzumab. Prescriptions from 1 January 2002 to 6 months post each patient's initiation to bendamustine were used in the analyses.

Assessing rituximab usage with bendamustine

Rituximab prescriptions supplied up to 2 years prior and 1 year post initiation to bendamustine were extracted from the DHS PBS prescription database for each patient that had bendamustine treatment. Patients with less than 12 months follow up post-initiation to bendamustine (i.e. initiators after the end of September 2017) were excluded from the analysis. There were 1,421 patients that remained in the analysis. The numbers of rituximab prescriptions post initiation to bendamustine were calculated to assess the likely extent of use of rituximab maintenance therapy. The lag between the last rituximab prescription and bendamustine commencement was used to assess possible use of bendamustine in rituximab-refractory lymphoma.

Results

Number of patients treated

Figure 1 shows the number of patients initiating and prevalent to PBS bendamustine treatment.

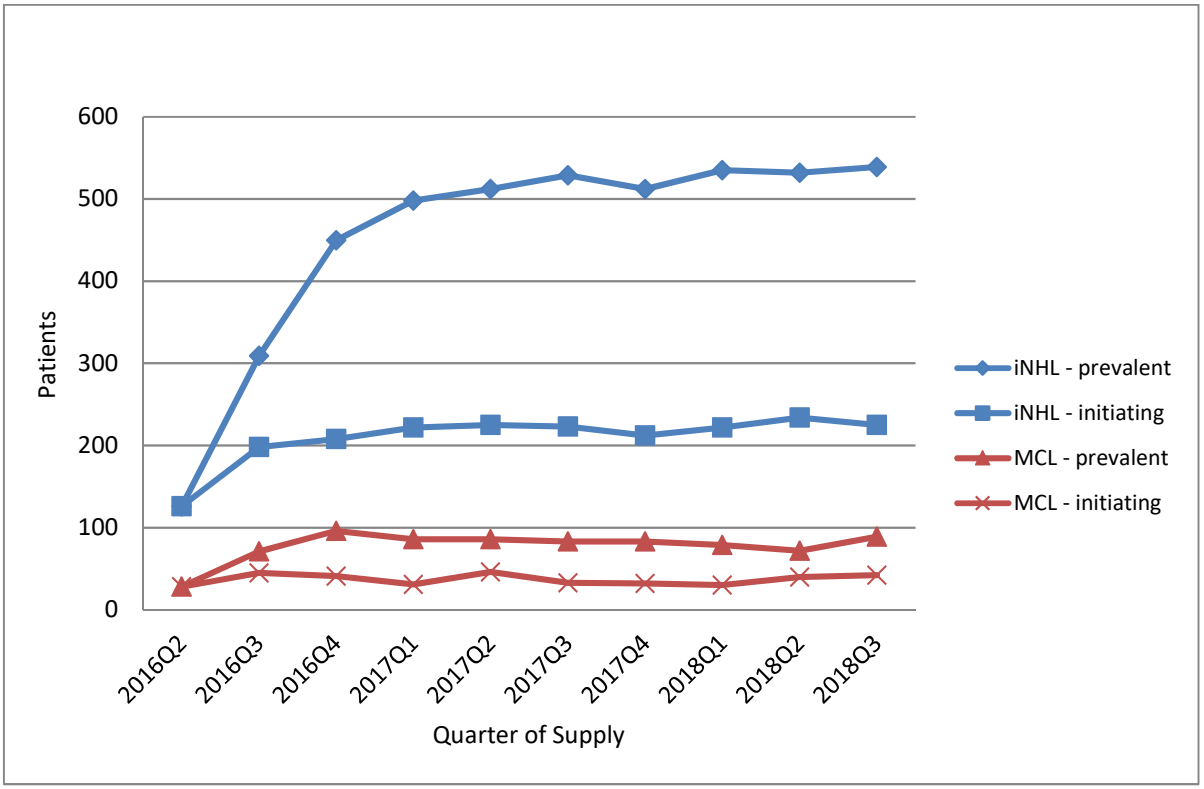

Figure 1: Patients initiating and prevalent to PBS bendamustine by indication
Sources: DHS prescription database (accessed 15 November 2018) and DHS authority approvals database.
Note: Patients with unknown indication (0.6%) have been excluded.

The number of initiating patients for iNHL and MCL had stabilised at approximately 225 and 35 per quarter, respectively. The number of prevalent patients for iNHL and MCL had stabilised at approximately 535 and 85 respectively.

Number of prescriptions

Figure 2 shows the utilisation of PBS prescriptions for bendamustine.

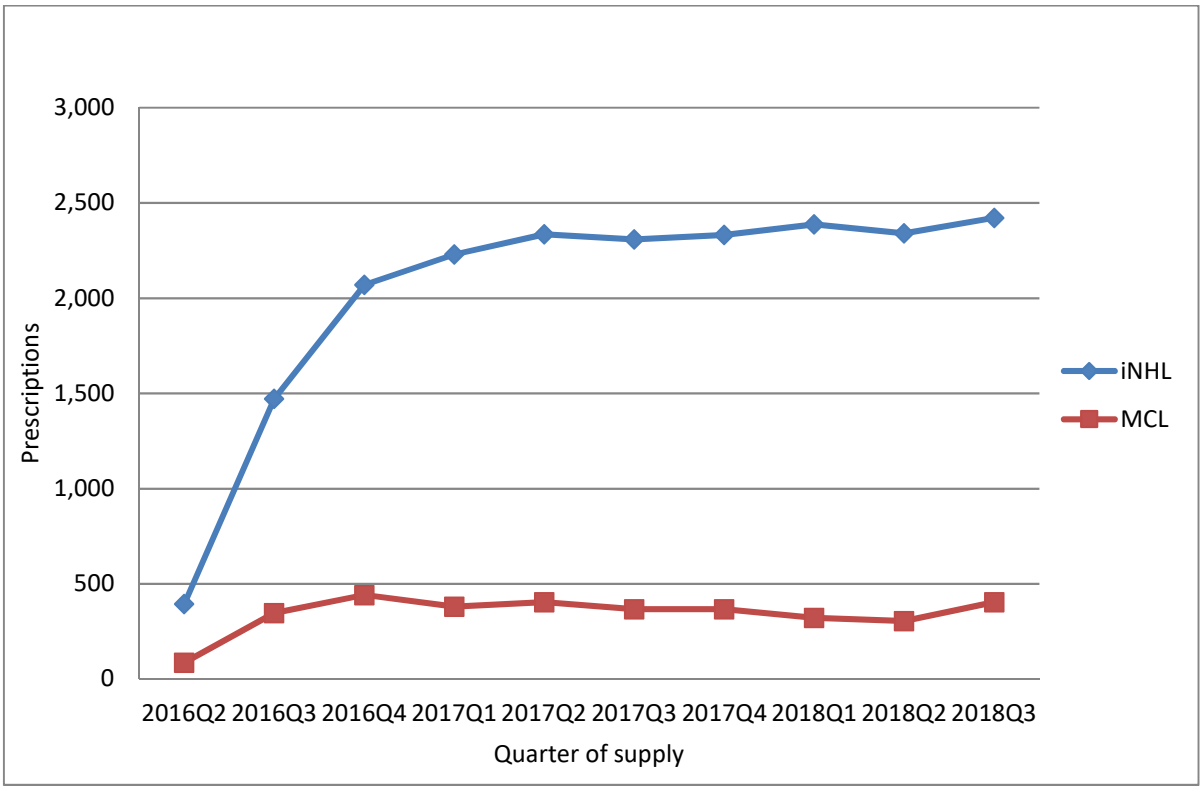

Figure 2: PBS prescriptions for bendamustine by indication

Source: DHS prescription database (accessed 15 November 2018). Note: bendamustine was listed on 1 May 2016 so 2016 Q2 only contains two months of data. Note: Prescriptions for patients with unknown indication (0.6%) have been excluded.

The number of prescriptions for iNHL and MCL had stabilised at approximately 2,350 and 360 per quarter respectively.

Predicted vs Actual analysis

Table 3: Predicted vs Actual analysis by indication

			Year1	Year 2
			May 16 to Apr 17	May 17 to Apr 18
Treated patients	indolent non-Hodgkin's lymphoma	Predicted (P)	[redacted]	[redacted]
		Actual (A)	816	1,182
		% Difference (A-P)/P	[redacted]	[redacted]
	mantle cell lymphoma	Predicted (P)	[redacted]	[redacted]
		Actual (A)	160	186
		% Difference (A-P)/P	[redacted]	[redacted]
	Total*	Predicted (P)	[redacted]	[redacted]
		Actual (A)	980	1,380
		% Difference (A-P)/P	[redacted]	[redacted]
Prescriptions	indolent non-Hodgkin's lymphoma	Predicted (P)	[redacted]	[redacted]
		Actual (A)	6,858	9,407
		% Difference (A-P)/P	[redacted]	[redacted]
	mantle cell lymphoma	Predicted (P)	[redacted]	[redacted]
		Actual (A)	1,363	1,431
		% Difference (A-P)/P	[redacted]	[redacted]
	Total*	Predicted (P)	[redacted]	[redacted]
		Actual (A)	8,249	10,932
		% Difference (A-P)/P	[redacted]	[redacted]
Prescriptions per patient	indolent non-Hodgkin's lymphoma	Predicted (P)	[redacted]	[redacted]
		Actual (A)	8.4	8.0
		% Difference (A-P)/P	[redacted]	[redacted]
	mantle cell lymphoma	Predicted (P)	[redacted]	[redacted]
		Actual (A)	8.5	7.7
		% Difference (A-P)/P	[redacted]	[redacted]
	Total*	Predicted (P)	[redacted]	[redacted]
		Actual (A)	8.4	7.9
		% Difference (A-P)/P	[redacted]	[redacted]
PBS + RPBS expenditure	Total	Predicted (P)	[redacted]	[redacted]
		Actual (A)	$12,890,750	$17,220,178
		% Difference (A-P)/P	[redacted]	[redacted]

Source: July 2015 Minor submission estimates spreadsheet (Attachment 2 Financial Estimates) with 2016 (Year 2 in the spreadsheet) as the first year of listing. Note: indications are that of the most common indication for each patient supplied in the period 1 May 2016 to the end of September 2018.
* Total includes patients with unknown indication.

In Year 1 the total number of patients supplied bendamustine was approximately the same as predicted. There were fewer iNHL patients but more MCL patients treated than expected. In Year 2 iNHL, MCL and total patients were more than predicted by [redacted]% respectively.

The higher number of patients treated did not lead to more than predicted prescriptions. The total number of prescriptions supplied was [redacted]% lower than expected in Years 1 and 2 respectively. The lower than expected number of prescriptions per patient per year can, in part, be explained by patients initiating toward the end of one listing year and completing their induction regimen in the following year. An assessment of the number of prescriptions per patient is presented later in the report.

PBS + RPBS expenditure was [redacted]% less than predicted in Year 1 and the same as predicted in Year 2.

Differences in the predicted and actual number of prescriptions and expenditure are approximately proportional, suggesting that the dose prescribed in practice has been similar to expected. The recommended dose in the Product Information for combination therapy with rituximab for first-line non-Hodgkin's lymphoma and mantle cell lymphoma is 90 mg/m^2. Doses may be reduced if non-haematological toxicities occur[2] or for older patients and those with renal impairment.[6] In the B-R arm of the STiL trial, full doses were received by 95.9% patients[7]. The submission assumed an average Body Surface Area (BSA) of 1.8 m^2 (based on Dooley 2004[8]) giving a predicted average dose of 162mg. Based on bendamustine prescriptions supplied from 1 May 2016 to 30 September 2018, the median and mean doses for MCL and iNHL were 170 and 167.5 mg, and 170 and 167.1 mg, respectively.

[6] UptoDate.com Accessed 16 December 2018.
[7] Bendamustine submission to the March 2015 PBAC, p95
[8] Dooley MJ, Singh S, Michael M: Implications of dose rounding of chemotherapy to the nearest vial size. Support Care Cancer. 2004, 12: 653-656.

Number of prescriptions in the first 12 months of treatment

The protocol for the StiL trial included 6 cycles of B-R induction (12 doses of B) treatment. The trial resulted in an average of 5.58 cycles (11.2 doses) per patient. The PBS restriction specifies that patients should not receive more than 6 cycles (12 doses). The mean number of doses per PBS patient in their first 12 months of treatment was 10.5 and 10.2 for iNHL and MCL patients respectively. The median number of doses for both MCL and iNHL was 12.

Figure 3 shows the distribution of prescriptions (infusions) of bendamustine per patient in their first 12 months of treatment. Patients who initiated treatment after the end of September 2017 were excluded from the analysis as they did not have a full 12 months of follow up.

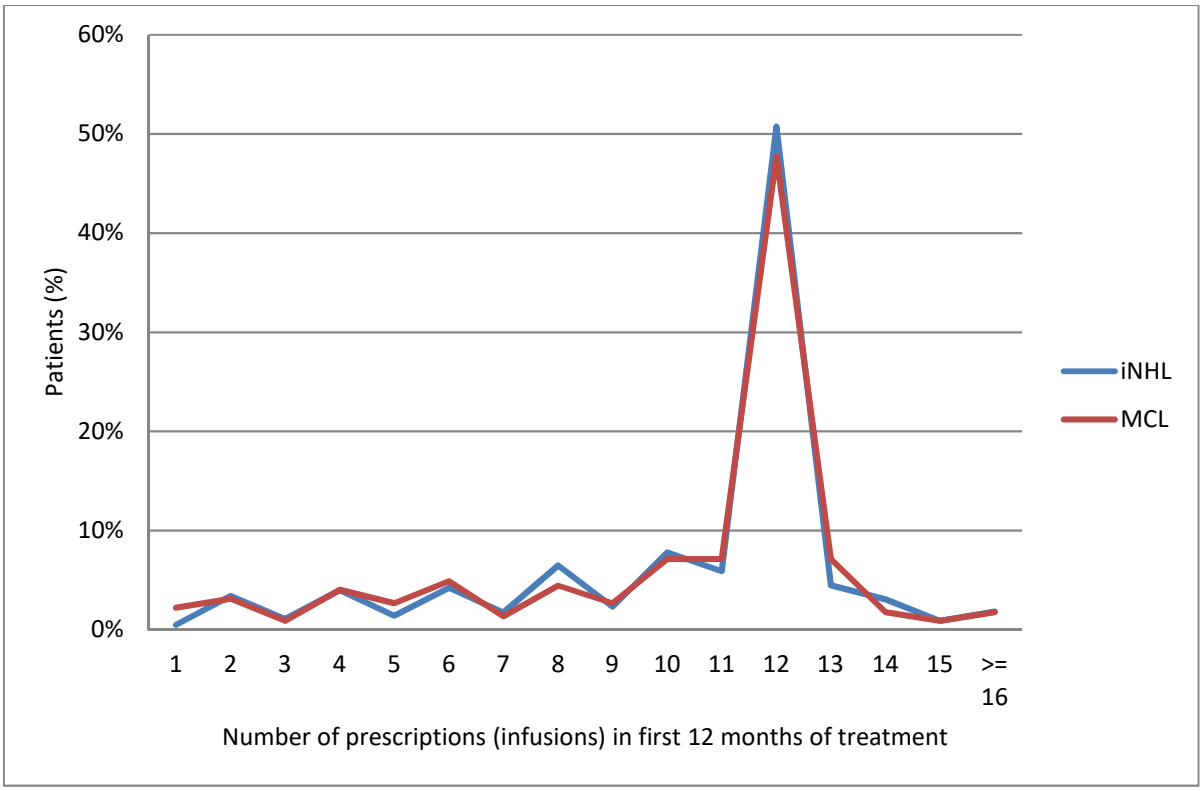

Figure 3: Distribution of number of infusions per patient in first 12 months of treatment by indication Source: DHS prescription database (accessed 15 November 2018)

Half of patients (50.3%) get 6 cycles (12 infusions) of treatment and 39.2% received less than 6 cycles of treatment in the first 12 months. There was a trend toward lower dose and fewer infusions in older patients (Figures 3 and 4).

Despite the restriction specifying that patients should not receive more than 6 cycles (12 doses) of bendamustine, 10.3% and 11.6% of iNHL and MCL patients respectively received more than 12 doses. As a Streamlined Authority, the requirement to limit use to 6 cycles relies on prescribers complying with the restriction.

Age variation of dose and number of cycles

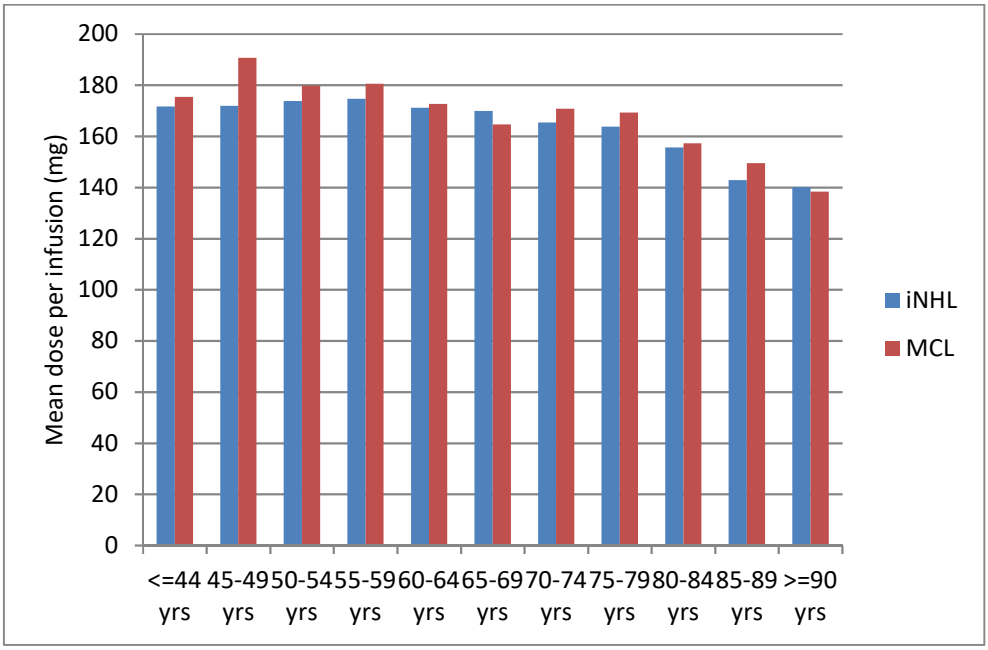

Figure 4: Mean infusion dose by patient age group

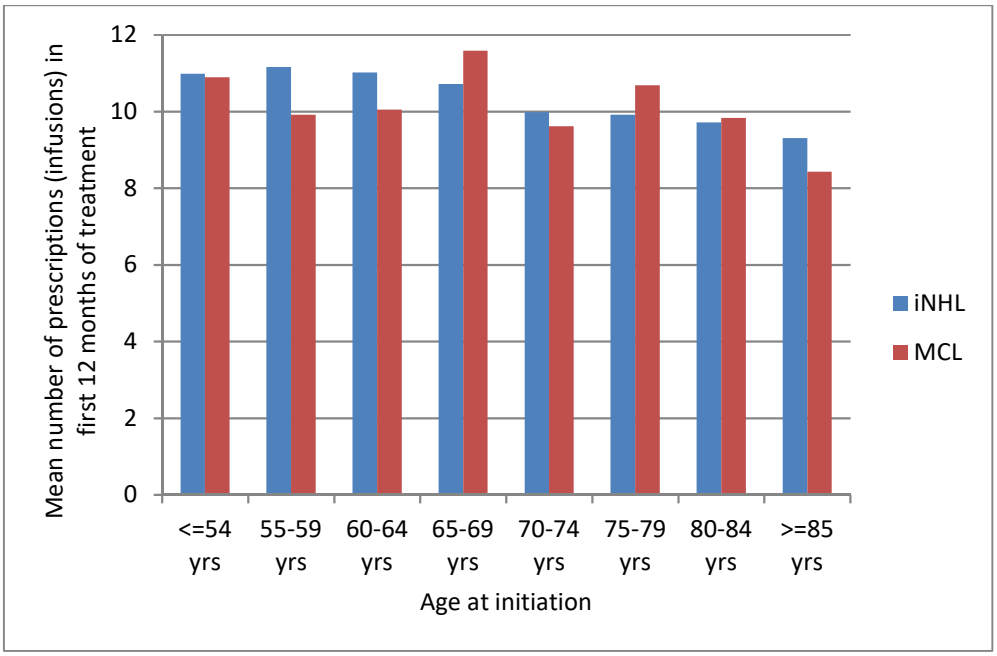

Figure 5: Mean number of infusions / prescriptions per patient in first 12 months of treatment by age group.

Medicine initiation sequence analysis

To assess if bendamustine was prescribed outside of the PBS restriction for previously treated iNHL or MCL or for non-subsidised indications such as CLL, medicine initiation sequences were determined. The medicines included in the analysis were bendamustine; rituximab; prednisolone, cyclophosphamide, vincristine, doxorubicin (CHOP or CVP); chlorambucil, fludarabine, ibrutinib, ofatumumab and obinutuzumab (used for CLL).

Table 4: Medicine initiation sequence, from January 2002 to 6 months post initiation to bendamustine for selected medicines.

Drug initiation sequence	Patients	% Patients	Rank
bendamustine -> rituximab(sd)	674	34.8%	1
prednisolone -> bendamustine -> rituximab(sd)	387	20.0%	2
rituximab -> bendamustine	186	9.6%	3
bendamustine -> rituximab	123	6.4%	4
prednisolone -> rituximab -> bendamustine	93	4.8%	5
prednisolone -> bendamustine -> rituximab	63	3.3%	6
bendamustine -> rituximab(sd) -> prednisolone	50	2.6%	7
rituximab -> bendamustine -> prednisolone	18	0.9%	8
cyclophosphamide -> vincristine(sd) -> rituximab -> bendamustine	10	0.5%	9
prednisolone -> cyclophosphamide -> doxorubicin(sd) -> rituximab(sd) -> vincristine(sd) -> bendamustine	9	0.5%	10
Bendamustine	8	0.4%	11
bendamustine -> rituximab -> prednisolone	7	0.4%	12
chlorambucil -> bendamustine -> rituximab(sd)	7	0.4%	13
chlorambucil -> rituximab -> bendamustine	7	0.4%	14
cyclophosphamide -> doxorubicin(sd) -> rituximab(sd) -> vincristine(sd) -> bendamustine	6	0.3%	15
cyclophosphamide -> doxorubicin(sd) -> vincristine(sd) -> rituximab -> bendamustine	6	0.3%	16
prednisolone -> rituximab -> cyclophosphamide -> doxorubicin(sd) -> vincristine(sd) -> bendamustine	6	0.3%	17
rituximab -> prednisolone -> bendamustine	6	0.3%	18
prednisolone -> cyclophosphamide -> rituximab(sd) -> vincristine(sd) -> bendamustine	5	0.3%	19
Other	265	13.7%	
Total	1,936	100%	

Note: (sd) = same day initiation (i.e. initiated drug on the same day as prior drug in the sequence).

Note: arrows indicate order of medicines appearing in the patients PBS dispensing history. Hospital and pharmacy dispensing practices may mean that not all components of treatment regimens are dispensed on the same day.

Analysis of the data for Table 4 shows that 84.5% of patients have sequences that only contain bendamustine, rituximab or prednisolone. This confirms that the majority of bendamustine use is within the restriction. However, bendamustine was also used outside of the restriction as demonstrated by:

- 3.8% of patients had prior cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) and 1.6% of patients had prior cyclophosphamide, vincristine, prednisolone

(CVP) indicating that these patients have received previous treatment for iNHL or MCL[9]. Overall, 5.4% of patients had prior CVP or CHOP;

- 3.8% of patients treated with bendamustine had at least one supply of a medicine for CLL (chlorambucil, ofatumumab, obinutuzumab or ibrutinib). 1.1% of patients were supplied fludarabine (and rituximab). In total 4.5% of patients were supplied any of these CLL medicines. Bendamustine is TGA registered but not PBS subsidised for treatment of CLL.

Overall, 190 patients (9.8%) had any of the above indicators of receiving bendamustine outside of the proposed restriction, either as they were previously treated for iNHL or are likely to have CLL (this does not double count patients that had more than one of the indicators).

[9] The analyses defined previous CHOP as a prior history of all 4 components of CHOP regimen or all three components of the CVP regimen. Prednisolone is inexpensive and may not be dispensed through the PBS as part of the CHOP or CVP regimen. The use of prior CHOP increases from 3.8% to 5.2% if CHOP was defined as prior PBS history of cyclophosphamide, doxorubicin, vincristine. Use of prior CVP increased from 1.6% to 2.7% if CVP was defined as prior cyclophosphamide and vincristine.

Assessing rituximab usage with bendamustine

Patterns of rituximab use before and/or after bendamustine gives insight into rituximab as maintenance therapy after B-R, or bendamustine for rituximab-refractory lymphoma.

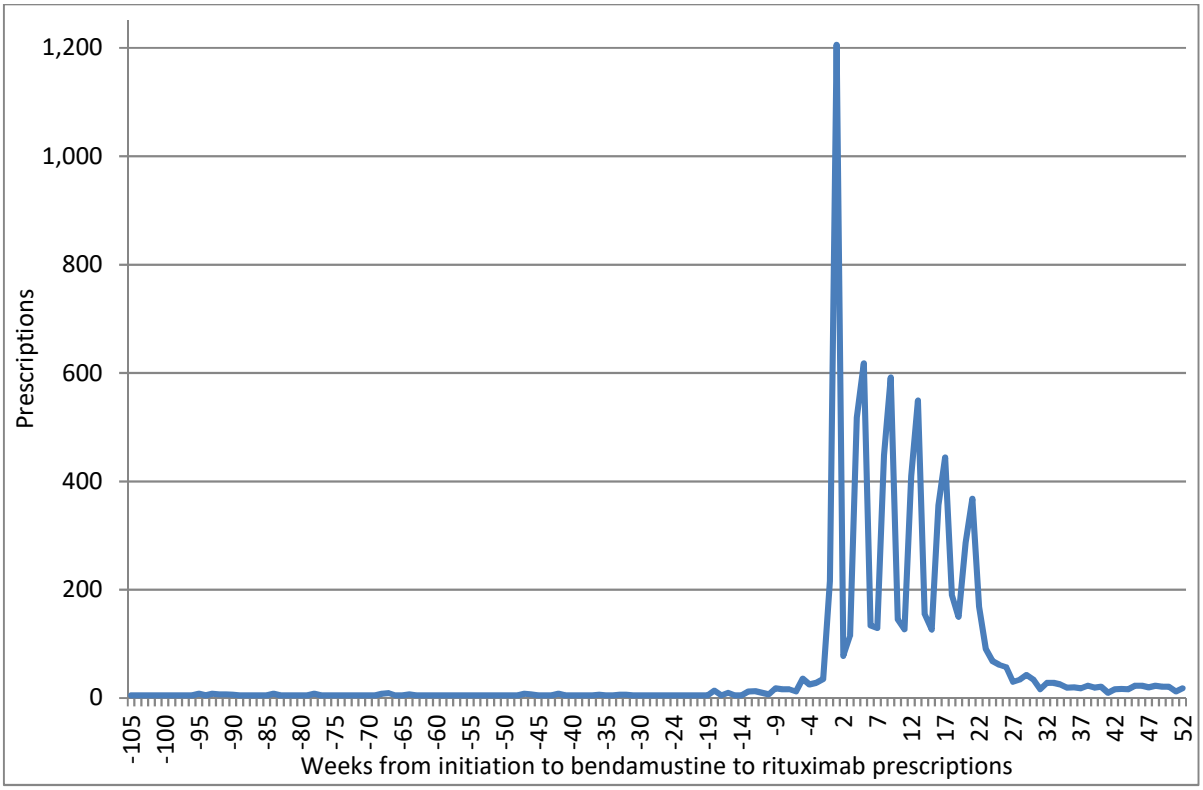

Figure 6: Weeks from initiation to bendamustine to rituximab prescriptions.
Note: only includes patients with at least 12 months follow up post-initiation to bendamustine (i.e. initiators up to the end of September 2017, n=1,421 patients). Where the prescription count is between 1 and 5 (inclusive), the data point has been set to 5 to protect confidentiality.

Figure 6 shows that there was little rituximab utilisation prior to the first bendamustine prescription. This is consistent with the bendamustine restriction criteria requiring the condition to be previously untreated. The increase in rituximab use in the weeks just before the first bendamustine script may be due to pharmacy dispensing and supply practices (the rituximab component of B-R dispensed on a separate day). A history of rituximab before bendamustine could also indicate use of bendamustine in the rituximab-refractory population.

In Figure 6 there are 24 patients (1.7%) whose last rituximab prescription prior to initiating bendamustine was more than 6 months prior. These patients could reasonably be classified as previously treated. There were 22 patients (1.5%) whose last rituximab was between 6 months and 6 weeks prior to initiating bendamustine. These patients could be considered to be rituximab-refractory if they had a partial response or progression while on or within 6 months after completion of a prior rituximab-containing regimen.

Figure 7 shows the distribution of the number of rituximab prescriptions per patient. One prescription of rituximab provides one cycle of treatment. Rituximab treatment decreases markedly after 6 cycles consistent with the B-R induction regimen.

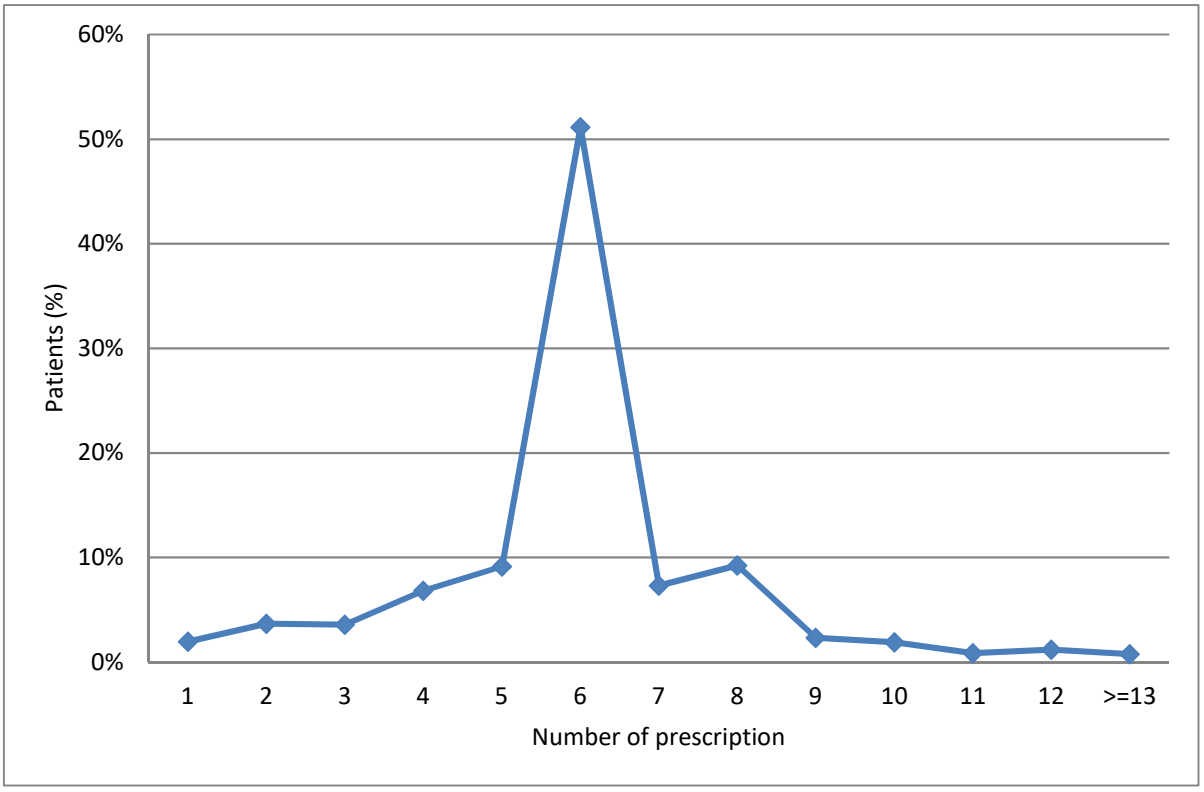

Figure 7: Distribution of rituximab prescriptions per patient in the period 5 weeks prior to and 12 months post initiation to bendamustine

Note: the analysis includes rituximab supplied from 5 weeks prior to and 12 months post initiation to bendamustine.

The submission assumed an average of 5.58 cycles of B-R. The mean and median numbers of prescriptions in Figure 7 are 6.00 and 6 prescriptions per patient respectively. 23% of patients had more than 6 prescriptions and 25% had less. Treatment with more than 6 prescriptions may be considered maintenance treatment which is outside the restriction for bendamustine.

In making its recommendation to list bendamustine on the PBS, the PBAC considered there would be reduced expenditure on rituximab maintenance and that listing of bendamustine on the PBS for first line therapy of iNHL and MCL 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. The PBAC considered, however, that these cost savings would not be realised in practice if maintenance therapy with rituximab was used following B-R induction therapy, noting that the cost-effectiveness of this approach had not been established.

DUSC consideration

DUSC considered that:

- The percentage differences between the predicted and actual number of prescriptions and expenditure were similar which suggests the dose prescribed in practice was approximately as expected.
- As prednisolone is inexpensive and not always supplied via the PBS, the estimate of 5.4% of bendamustine patients having prior CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) or CVP (cyclophosphamide, vincristine, prednisolone) was a conservative estimate. That is, patients supplied PBS cyclophosphamide, doxorubicin and vincristine may well be on CHOP with the prednisolone component funded by a clinic or hospital.
- Some of the 23% of patients receiving more than 6 rituximab prescriptions may not be on rituximab maintenance therapy. Instead they may be the 10.5% of patients that had more than 6 cycles of bendamustine + rituximab. Thus a better estimate of the proportion of patients on rituximab maintenance therapy may be 23% – 10.5% = 12.5%.
- The sponsor's Pre-Sub Committee Response (PSCR) suggested that one possible cause of patients receiving more than 6 prescriptions of rituximab was that that the protocol in the BRIGHT trial allowed a maximum of 8 cycles, whereas the PBS restriction, which limits use to 6 cycles, is based on the STiL trial. DUSC considered that this was a plausible explanation of why some patients received 8 prescriptions of rituximab.
- In their PSCR the Sponsor noted that, in response to PBAC's concern about leakage into treatment of CLL, they had previously offered to;
  - have an Authority Required – Telephone restriction level, instead of the current Streamlined Authority.
  - add a note to the restriction to the effect of "bendamustine is not PBS subsidised for the treatment of CLL".

  DUSC was of the view that with the low and likely declining use of bendamustine outside of the proposed restriction that this may not be warranted and referred this matter to the PBAC for consideration.
- The report requested that the Sponsor advise the PBAC if a submission for bendamustine for the treatment of CLL would be forthcoming. The PSCR advised that they did not intend to seek such a listing for bendamustine as "there are more clinically effective drugs listed on the PBS for CLL patients (i.e. ibrutinib and obinutuzumab) and there may not be a position for bendamustine in this market. DUSC agreed that this is the case and considered that the place for bendamustine in treatment of CLL was likely to be limited. DUSC referred this matter to the PBAC.

DUSC actions

The report, Sponsor responses and DUSC minutes were referred to the PBAC.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsors' comments

Janssen-Cilag Pty Ltd (Ribomustin®): The sponsor has no comment.

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

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